



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/19, 31/215, 31/34, 31/44</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 97/24116</b> <b>(43) International Publication Date:</b> 10 July 1997 (10.07.97)
<b>(21) International Application Number:</b> PCT/US96/20511 <b>(22) International Filing Date:</b> 16 December 1996 (16.12.96)  <b>(30) Priority Data:</b> 08/580,553 29 December 1995 (29.12.95) US  <b>(71) Applicant:</b> ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US).  <b>(72) Inventors:</b> TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US).  <b>(74) Agents:</b> BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-2,2-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR <sub>α</sub> RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY  <b>(57) Abstract</b>  Retinoid compounds which act specifically or selectively on RAR <sub>α</sub> receptor subtypes in preference over RAR <sub>β</sub> and RAR <sub>γ</sub> receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.		

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1       **METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR<sub>α</sub>**  
2       **RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY**

3               **BACKGROUND OF THE INVENTION**

4           1.   Field of the Invention

5           The present invention relates to the use of  
6   compounds which have specific or selective agonist  
7   like activity on RAR<sub>α</sub> retinoid receptors for  
8   treatment of diseases and conditions which respond  
9   to treatment by such retinoids. More particularly  
10   the present invention is directed to the use of RAR<sub>α</sub>  
11   receptor specific or selective agents for the  
12   treatment of tumors.

13          2.   Background Art

14          Compounds which have retinoid-like activity are  
15   well known in the art, and are described in numerous  
16   United States and other patents and in scientific  
17   publications. It is generally known and accepted in  
18   the art that retinoid-like activity is useful for  
19   treating animals of the mammalian species, including  
20   humans, for curing or alleviating the symptoms and  
21   conditions of numerous diseases and conditions. In  
22   other words, it is generally accepted in the art  
23   that pharmaceutical compositions having a  
24   retinoid-like compound or compounds as the active  
25   ingredient are useful as regulators of cell  
26   proliferation and differentiation, and particularly  
27   as agents for treating skin-related diseases,  
28   including, actinic keratoses, arsenic keratoses,  
29   inflammatory and non-inflammatory acne, psoriasis,  
30   ichthyoses and other keratinization and  
31   hyperproliferative disorders of the skin, eczema,  
32   atopic dermatitis, Darriers disease, lichen planus,  
33   prevention and reversal of glucocorticoid damage  
34   (steroid atrophy), as a topical anti-microbial, as  
35   skin anti-pigmentation agents and to treat and

1 reverse the effects of age and photo damage to the  
2 skin. Retinoid compounds are also useful for the  
3 prevention and treatment of cancerous and  
4 precancerous conditions, including, premalignant and  
5 malignant hyperproliferative diseases such as  
6 cancers of the breast, skin, prostate, cervix,  
7 uterus, colon, bladder, esophagus, stomach, lung,  
8 larynx, oral cavity, blood and lymphatic system,  
9 metaplasias, dysplasias, neoplasias, leukoplakias  
10 and papillomas of the mucous membranes and in the  
11 treatment of Kaposi's sarcoma. In addition,  
12 retinoid compounds can be used as agents to treat  
13 diseases of the eye, including, without limitation,  
14 proliferative vitreoretinopathy (PVR), retinal  
15 detachment, dry eye and other corneopathies, as well  
16 as in the treatment and prevention of various  
17 cardiovascular diseases, including, without  
18 limitation, diseases associated with lipid  
19 metabolism such as dyslipidemias, prevention of  
20 post-angioplasty restenosis and as an agent to  
21 increase the level of circulating tissue plasminogen  
22 activator (TPA). Other uses for retinoid compounds  
23 include the prevention and treatment of conditions  
24 and diseases associated with human papilloma virus  
25 (HPV), including warts and genital warts, various  
26 inflammatory diseases such as pulmonary fibrosis,  
27 ileitis, colitis and Krohn's disease,  
28 neurodegenerative diseases such as Alzheimer's  
29 disease, Parkinson's disease and stroke, improper  
30 pituitary function, including insufficient  
31 production of growth hormone, modulation of  
32 apoptosis, including both the induction of apoptosis  
33 and inhibition of T-cell activated apoptosis,  
34 restoration of hair growth, including combination



1 therapies with the present compounds and other  
2 agents such as Minoxidil<sup>R</sup>, diseases associated with  
3 the immune system, including use of the present  
4 compounds as immunosuppressants and  
5 immunostimulants, modulation of organ transplant  
6 rejection and facilitation of wound healing,  
7 including modulation of chelosis.

8 United States Patent Nos. 4,740,519 (Shroot et  
9 al.), 4,826,969 (Maignan et al.), 4,326,055  
10 (Loeliger et al.), 5,130,335 (Chandraratna et al.),  
11 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et  
12 al.), 5,324,840 (Chandraratna), 5,344,959  
13 (Chandraratna), 5,130,335 (Chandraratna et al.),  
14 Published European Patent Application Nos. 0 170 105  
15 (Shudo), 0 176 034 A (Wuest et al.), 0 350 846 A  
16 (Klaus et al.), 0 176 032 A (Frickel et al.), 0 176  
17 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),  
18 0 303 915 A (Bryce et al.), UK Patent Application GB  
19 2190378 A (Klaus et al.), German Patent Application  
20 Nos. DE 3715955 A1 (Klaus et al.), DE 3602473 A1  
21 (Wuest et al., and the articles J. Amer. Acad. Derm.  
22 15: 756 - 764 (1986) (Sporn et al.), Chem. Pharm.  
23 Bull. 33: 404-407 (1985) (Shudo et al.), J. Med  
24 Chem. 1988 31, 2182 - 2192 (Kagechika et al.),  
25 Chemistry and Biology of Synthetic Retinoids CRC  
26 Press Inc. 1990 p 334 - 335, 354 (Dawson et al.),  
27 describe or relate to compounds which include a  
28 tetrahydronaphthyl moiety and have retinoid-like or  
29 related biological activity.

30 United States Patent Nos. 4,980,369, 5,006,550,  
31 5,015,658, 5,045,551, 5,089,509, 5,134,159,  
32 5,162,546, 5,234,926, 5,248,777, 5,264,578,  
33 5,272,156, 5,278,318, 5,324,744, 5,346,895,  
34 5,346,915, 5,348,972, 5,348,975, 5,380,877,

1 5,399,561, 5,407,937, (assigned to the same assignee  
2 as the present application) and patents and  
3 publications cited therein, describe or relate to  
4 chroman, thiochroman and 1,2,3,4-tetrahydroquinoline  
5 derivatives which have retinoid-like biological  
6 activity.

7 United States Patent No. 4,723,028 (Shudo),  
8 Published European Patent Application Nos. 0 170 105  
9 (Shudo), German Patent Application No. DE 3524199 A1  
10 (Shudo), PCT WO 91/16051 (Spada et al.), PCT WO  
11 85/04652 (Polus) and J. Med Chem. 1988 31, 2182 -  
12 2192 (Kagechika et al.), describe or relate to aryl  
13 and heteroaryl or diaryl substituted olephines or  
14 amides having retinoid-like or related biological  
15 activity.

16 United States Patent Nos. 4,992,468, 5,013,744,  
17 5,068,252, 5,175,185, 5,202,471, 5,264,456,  
18 5,324,840, 5,326,898, 5,349,105, 5,391,753,  
19 5,414,007 and 5,434,173 (assigned to the same  
20 assignee as the present application) and patents and  
21 publications cited therein, describe or relate to  
22 compounds which have retinoid-like biological  
23 activity and a structure wherein a phenyl and a  
24 heteroaryl or a phenyl and a second phenyl group is  
25 linked with an olephinic or acetylenic linkage.  
26 Still further, several co-pending applications and  
27 recently issued patents which are assigned to the  
28 assignee of the present application, are directed to  
29 further compounds having retinoid-like activity.

30 It is now general knowledge in the art that two  
31 main types of retinoid receptors exist in mammals  
32 (and other organisms). The two main types or  
33 families of receptors are respectively designated  
34 RARs and RXRs. Within each type there are subtypes;

1 in the RAR family the subtypes are designated  $RAR_\alpha$ ,  
2  $RAR_\beta$  and  $RAR_\gamma$ , in RXR the subtypes are:  $RXR_\alpha$ ,  $RXR_\beta$  and  
3  $RXR_\gamma$ . It has also been established in the art that  
4 the distribution of the two main retinoid receptor  
5 types, and of the several sub-types is not uniform  
6 in the various tissues and organs of mammalian  
7 organisms.

8 It is also known in the art that the use of  
9 retinoid-like compounds for the treatment of various  
10 diseases and conditions is not without problems or  
11 side effects. The side effects at therapeutic dose  
12 levels include headache, teratogenesis,  
13 mucocutaneous toxicity, musculoskeletal toxicity,  
14 dislipidemias, skin irritation, headache,  
15 hepatotoxicity, etc. These side effects limit the  
16 acceptability and utility of retinoids for treating  
17 disease. Research is still ongoing in the art to  
18 determine which of the RAR or RXR families and within  
19 each family, which of the subtype or subtypes are  
20 responsible for mediating certain therapeutic  
21 effects, and which type or subtypes are responsible  
22 for mediating one or more of the undesired side  
23 effects. Accordingly, among compounds capable of  
24 binding to retinoid receptors, specificity or  
25 selectivity for one of the main types or families,  
26 and even specificity or selectivity for one or more  
27 subtypes within a family of receptors, is considered  
28 a desirable pharmacological property. Such  
29 selectivity or specificity is useful as a research  
30 tool for discovering the roles of the several  
31 receptor types and subtypes in mediating the various  
32 effects of retinoids in biological systems, and also  
33 as aid for designing retinoid drugs with specific  
34 therapeutic effects and/or with reduced side effects

1 and toxicity. Along these lines, United States  
2 Patent No. 5,324,840 describes a class of compounds  
3 in which retinoid-like activity is accompanied by  
4 reduced skin toxicity and reduced teratogenic  
5 effects. United States Patent No. 5,399,586  
6 describes the use of compounds having RXR retinoid  
7 receptor agonist activity for the treatment of  
8 mammals afflicted with tumors. United States Patent  
9 No. 5,455,265 describes methods of treatment of  
10 mammals with compounds having agonist-like activity  
11 on RXR receptors. Published PCT application No.  
12 WO93/11755 is also directed to the use of compounds  
13 which are selective RXR receptor agonists.

14 The present invention provides methods of  
15 treatment of tumors with compounds which are  
16 specific or selective to  $RAR_{\alpha}$  receptors.

17 **SUMMARY OF THE INVENTION** It has been  
18 discovered in accordance with the present invention  
19 that retinoid-like compounds which act selectively,  
20 or preferably even specifically on  $RAR_{\alpha}$  receptor  
21 subtypes in preference over  $RAR_{\beta}$  and  $RAR_{\gamma}$  receptor  
22 subtypes, possess desirable pharmaceutical  
23 properties associated with retinoids, and are  
24 particularly suitable for treatment of tumors, such  
25 as acute monocytic leukemia, cervical carcinoma,  
26 myeloma, ovarian carcinomas and head and neck  
27 carcinomas, without having one or more undesirable  
28 side effects of retinoids, such as inducement of  
29 weight loss, mucocutaneous toxicity, skin irritation  
30 and teratogenecity.

31 Accordingly, the present invention relates to  
32 the use of  $RAR_{\alpha}$  specific or selective retinoid  
33 compounds for the treatment of diseases and  
34 conditions which respond to treatment by such

1 compounds, and particularly to the treatment of  
2 tumors, primarily acute monocytic leukemia, cervical  
3 carcinoma, myeloma, ovarian carcinomas and head and  
4 neck carcinomas with the  $RAR_{\alpha}$  specific or selective  
5 retinoid compounds. In accordance with the present  
6 invention the  $RAR_{\alpha}$  selective compounds are also  
7 particularly advantageously used for treatment of  
8 proliferative vitreoretinopathy (PVR) and age  
9 related macular degeneration (AMD).

10 For the purposes of the present description a  
11 compound is considered  $RAR_{\alpha}$  specific or selective if  
12 in a transactivation assay (described below) the  
13 compound transactivates the  $RAR_{\alpha}$  receptors at a  
14 significantly lower concentration than the  $RAR_{\beta}$  and  
15  $RAR_{\gamma}$  receptors. Instead of measuring  
16 transactivation, measuring the binding of a compound  
17 respectively to the three RAR receptor subtypes is  
18 also feasible. Binding data expressed in Kd numbers  
19 obtained in a binding assay (described below) are  
20 also indicative of a compound's ability to act  
21 specifically or selectively on  $RAR_{\alpha}$  receptors in  
22 preference over  $RAR_{\beta}$  and  $RAR_{\gamma}$  receptors. A compound  
23 is considered  $RAR_{\alpha}$  specific or selective for the  
24 purposes of the present invention if the Kd number  
25 for its binding to  $RAR_{\alpha}$  receptors is approximately  
26 500 times smaller than the Kd for its affinity to  
27  $RAR_{\beta}$  and  $RAR_{\gamma}$  receptors.

#### 28 BRIEF DESCRIPTION OF THE DRAWING FIGURES

29 Figure 1 is a graph showing the results of an RPMI  
30 8226 cell culture assay conducted with all trans  
31 retinoic acid (ATRA) and two  $RAR_{\alpha}$  selective compounds  
32 in accordance with the present invention.

33 Figure 2 is another graph showing the results of  
34 an AML 193 cell culture assay conducted with two  $RAR_{\alpha}$

1 selective compounds in accordance with the present  
2 invention, and with two compounds which are not RAR<sub>α</sub>  
3 selective.

4 **Figure 3** is still another graph showing results  
5 of an AML 193 cell culture assay conducted with  
6 three RAR<sub>α</sub> selective compounds in accordance with the  
7 present invention and with all trans retinoic acid  
8 (ATRA).

9 **Figure 4** is a graph showing the proliferation of  
10 ovarian tumor cells in a cell culture assay (EDR  
11 assay) in the presence of varying concentrations of  
12 **Compound 2** in accordance with the present invention.

13 **Figure 5** is a graph showing the RPE cell  
14 proliferation in the presence of all trans retinoic  
15 acid or **Compound 42** in the culture medium.

16 **Figure 6** is a graph showing the weight of a  
17 group of experimental rats which were administered  
18 for 3 days varying doses of an RAR<sub>α</sub> selective  
19 compound in accordance with the present invention.

20 **Figure 7** is a bar graph showing the weight of  
21 a group of experimental rats at the end of a 4 day  
22 period wherein for three days the rats were  
23 administered varying doses of **Compound 18** in  
24 accordance with the invention;

25 **Figure 8** is a graph showing the weight of guinea  
26 pigs which were treated with varying doses of  
27 **Compound 42** for 15 days.

28 **DETAILED DESCRIPTION OF THE INVENTION** General  
29 **Embodiments** Definitions regarding the chemical  
30 compounds used in the present invention

31 The term alkyl refers to and covers any and all  
32 groups which are known as normal alkyl,  
33 branched-chain alkyl and cycloalkyl. The term  
34 alkenyl refers to and covers normal alkenyl, branch

1 chain alkenyl and cycloalkenyl groups having one or  
2 more sites of unsaturation. Similarly, the term  
3 alkynyl refers to and covers normal alkynyl, and  
4 branch chain alkynyl groups having one or more  
5 triple bonds.

6 Lower alkyl means the above-defined broad  
7 definition of alkyl groups having 1 to 6 carbons in  
8 case of normal lower alkyl, and as applicable 3 to 6  
9 carbons for lower branch chained and cycloalkyl  
10 groups. Lower alkenyl is defined similarly having 2  
11 to 6 carbons for normal lower alkenyl groups, and 3  
12 to 6 carbons for branch chained and cyclo- lower  
13 alkenyl groups. Lower alkynyl is also defined  
14 similarly, having 2 to 6 carbons for normal lower  
15 alkynyl groups, and 4 to 6 carbons for branch  
16 chained lower alkynyl groups.

17 The term "ester" as used here refers to and  
18 covers any compound falling within the definition of  
19 that term as classically used in organic chemistry.  
20 It includes organic and inorganic esters. Where B  
21 in the general formula of the preferred compounds  
22 used in the invention is  $\text{-COOH}$ , this term covers the  
23 products derived from treatment of this function  
24 with alcohols or thioalcohols preferably with  
25 aliphatic alcohols having 1-6 carbons. Where the  
26 ester is derived from compounds where B is  $\text{-CH}_2\text{OH}$ ,  
27 this term covers compounds derived from organic  
28 acids capable of forming esters including  
29 phosphorous based and sulfur based acids, or  
30 compounds of the formula  $\text{-CH}_2\text{OCOR}_{11}$  where  $\text{R}_{11}$  is any  
31 substituted or unsubstituted aliphatic, aromatic,  
32 heteroaromatic or aliphatic aromatic group,  
33 preferably with 1-6 carbons in the aliphatic  
34 portions.

1 Unless stated otherwise in this application,  
2 preferred esters are derived from the saturated  
3 aliphatic alcohols or acids of ten or fewer carbon  
4 atoms or the cyclic or saturated aliphatic cyclic  
5 alcohols and acids of 5 to 10 carbon atoms.  
6 Particularly preferred aliphatic esters are those  
7 derived from lower alkyl acids and alcohols. Also  
8 preferred are the phenyl or lower alkyl phenyl  
9 esters.

10 Amides has the meaning classically accorded that  
11 term in organic chemistry. In this instance it  
12 includes the unsubstituted amides and all aliphatic  
13 and aromatic mono- and di- substituted amides.  
14 Unless stated otherwise in this application,  
15 preferred amides are the mono- and di-substituted  
16 amides derived from the saturated aliphatic radicals  
17 of ten or fewer carbon atoms or the cyclic or  
18 saturated aliphatic-cyclic radicals of 5 to 10  
19 carbon atoms. Particularly preferred amides are  
20 those derived from substituted and unsubstituted  
21 lower alkyl amines. Also preferred are mono- and  
22 disubstituted amides derived from the substituted  
23 and unsubstituted phenyl or lower alkylphenyl  
24 amines. Unsubstituted amides are also preferred.

25 Acetals and ketals include the radicals of the  
26 formula-CK where K is  $(-OR)_2$ . Here, R is lower  
27 alkyl. Also, K may be  $-OR_1O-$  where  $R_1$  is lower alkyl  
28 of 2-5 carbon atoms, straight chain or branched.

29 A pharmaceutically acceptable salt may be  
30 prepared for any compound used in this invention  
31 having a functionality capable of forming such-salt,  
32 for example an acid functionality. A  
33 pharmaceutically acceptable salt is any salt which  
34 retains the activity of the parent compound and does



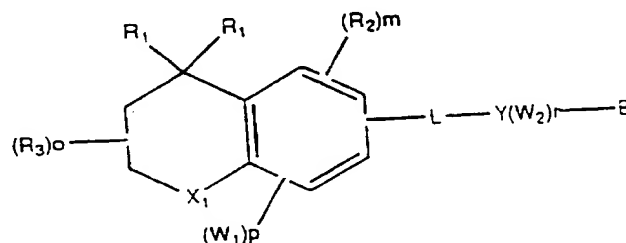
1 not impart any deleterious or untoward effect on the  
2 subject to which it is administered and in the  
3 context in which it is administered.  
4 Pharmaceutically acceptable salts may be derived  
5 from organic or inorganic bases. The salt may be a  
6 mono or polyvalent ion. Of particular interest are  
7 the inorganic ions, sodium, potassium, calcium, and  
8 magnesium. Organic salts may be made with  
9 amines, particularly ammonium salts such as mono-,  
10 di- and trialkyl amines or ethanol amines. Salts  
11 may also be formed with caffeine, tromethamine and  
12 similar molecules. Where there is a nitrogen  
13 sufficiently basic as to be capable of forming acid  
14 addition salts, such may be formed with any  
15 inorganic or organic acids or alkylating agent such  
16 as methyl iodide. Preferred salts are those formed  
17 with inorganic acids such as hydrochloric acid,  
18 sulfuric acid or phosphoric acid. Any of a number  
19 of simple organic acids such as mono-, di- or tri-  
20 acid may also be used.

21 Some of the compounds used in the present  
22 invention may have trans and cis (E and Z) isomers.  
23 In addition, the compounds used in the present  
24 invention may contain one or more chiral centers and  
25 therefore may exist in enantiomeric and  
26 diastereomeric forms. The scope of the present  
27 invention is intended to cover the use of all such  
28 isomers per se, as well as mixtures of cis and trans  
29 isomers, mixtures of diastereomers and racemic  
30 mixtures of enantiomers (optical isomers) as well.  
31 Description of the Compounds Preferably Used in the  
32 Methods of the Invention

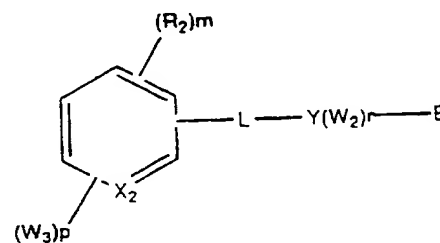
33 The retinoid-like compounds used in the methods  
34 of treatment of the present invention are specific

1 or selective for  $RAR_\alpha$  receptors. That a compound is  
 2 specific or selective to  $RAR_\alpha$  receptors can be  
 3 ascertained in transactivation assays described  
 4 below where an  $RAR_\alpha$  specific or selective compound  
 5 transactivates  $RAR_\alpha$  receptors at a significantly  
 6 lower concentrations than  $RAR_\beta$  or  $RAR_\gamma$  receptors. In  
 7 a binding assay where the ability of the compound to  
 8 bind to these receptor subtypes is measured, a  
 9 compound that is considered  $RAR_\alpha$  specific or  
 10 selective for the purposes of the present invention  
 11 binds at least approximately 500 times stronger to  
 12  $RAR_\alpha$  receptors than to the  $RAR_\beta$  or  $RAR_\gamma$  receptors.  
 13 Alternatively, the compound is considered  $RAR_\alpha$   
 14 specific or selective if in the binding assay its Kd  
 15 number is approximately in the  $10^{-1}$  to  $5 \times 10^2$   
 16 nanomolar range and the Kd number for  $RAR_\beta$  or  $RAR_\gamma$   
 17 receptors is greater than 1000 nanmolar. The latter  
 18 is indicated by 0.00 in the below provided Tables  
 19 where binding data (Kd numbers) for certain  
 20 exemplary compounds of the present invention are  
 21 illustrated.

22 Examples for  $RAR_\alpha$  selective compounds which are  
 23 preferably used in accordance with the present  
 24 invention are illustrated by Formula 1 and Formula 2



Formula 1



Formula 2

1 where  $X_1$  is O or  $X_1$  is  $[C(R_1)]_n$ , where  $n$  is an integer  
2 between 0 and 2;

3  $R_1$  is independently H or alkyl of 1 to 6  
4 carbons;

5  $R_2$  is independently hydrogen, or lower alkyl of  
6 1 to 6 carbons;

7  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or  
8 F;

9  $m$  is an integer having the value of 0 - 5;

10  $o$  is an integer having the value of 0 - 4;

11  $p$  is an integer having the value of 0 - 2;

12  $r$  is an integer having the value 0 - 2;

13  $X_2$  is N or CH;

14  $Y$  is a phenyl or naphthyl group, or heteroaryl  
15 selected from a group consisting of pyridyl,  
16 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
17 thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said  
18 phenyl, naphthyl and heteroaryl groups being  
19 optionally substituted with one or two  $R_2$  groups;

20  $W_1$  is a substituent selected independently from  
21 the group consisting of F, Br, Cl, I, fluoro  
22 substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH, with the provisos  
23 that:

24 (i) when the compound is in accordance with  
25 **Formula 1** and  $Z$  is O then the sum of  $p$  and  $r$  is at  
26 least 1 and  $W_1$  is not a fluoro group in the 3  
27 position of a tetrahydronaphthalene ring;

28 (ii) when the compound is in accordance with  
29 **Formula 1** and  $r$  is zero and  $p$  is 1 and  $W_1$  is OH then  
30 the OH group is positioned  $\alpha$  to the L group;

31  $W_2$  is a substituent selected independently from  
32 the group consisting of F, Br, Cl, I, fluoro  
33 substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH;

34  $W_3$  is a substituent selected independently from

1 the group consisting of F, Br, Cl, I, C<sub>1-6</sub>alkyl,  
2 fluoro substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH with the  
3 proviso that when the compound is in accordance with  
4 **Formula 2** and X<sub>2</sub> is CH and r is 0 then p is not 0 and  
5 at least one W<sub>3</sub> group is not alkyl;

6 L is -(C=Z)-NH- or -NH-(C=Z)-

7 Z is O or S, and

8 B is COOH or a pharmaceutically acceptable salt  
9 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>,  
10 CHO, CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O,  
11 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group  
12 containing 1 to 5 carbons, R<sub>8</sub> is an alkyl group of 1  
13 to 10 carbons or trimethylsilylalkyl where the alkyl  
14 group has 1 to 10 carbons, or a cycloalkyl group of  
15 5 to 10 carbons, or R<sub>8</sub> is phenyl or lower  
16 alkylphenyl, R<sub>9</sub> and R<sub>10</sub> independently are hydrogen,  
17 an alkyl group of 1 to 10 carbons, or a cycloalkyl  
18 group of 5-10 carbons, or phenyl or lower  
19 alkylphenyl, R<sub>11</sub> is lower alkyl, phenyl or lower  
20 alkylphenyl, R<sub>12</sub> is lower alkyl, and R<sub>13</sub> is divalent  
21 alkyl radical of 2-5 carbons.

22 With reference to symbol X<sub>1</sub> in **Formula 1**,  
23 compounds are preferred in the methods of the  
24 present invention where X<sub>1</sub> is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> and n is 1  
25 (tetrahydronaphthalene derivatives) and also where X<sub>1</sub>  
26 is O (chroman derivatives). With reference to the  
27 symbol X<sub>2</sub> in **Formula 2**, compounds are equally  
28 preferred where X<sub>2</sub> is CH or N. When X<sub>2</sub> is CH then  
29 the benzene ring is preferably 1, 3, 5 substituted  
30 with the L group occupying the 1 position and the W<sub>3</sub>  
31 and/or R<sub>2</sub> groups occupying the 3 and 5 positions.  
32 When the symbol X<sub>2</sub> is N, then the pyridine ring is  
33 preferably 2,4,6 substituted with the L group  
34 occupying the 4 position and the W<sub>3</sub> and/or R<sub>2</sub> groups

1 occupying the 2 and 6 positions.

2 The  $R_1$  groups of Formula 1 are preferably H or  
3  $\text{CH}_3$ . The  $R_2$  group of Formula 1 is preferably H. The  
4 group B of the preferred compounds of the invention  
5 is  $\text{COOH}$  or a pharmaceutically acceptable salt  
6 thereof,  $\text{COOR}_8$  or  $\text{CONR}_9\text{R}_{10}$ , where  $R_8$ ,  $R_9$  and  $R_{10}$  are  
7 defined as above.

8 Referring now to the  $W_1$  and  $W_2$  groups in Formula  
9 1, these groups are, generally speaking, electron  
10 withdrawing groups, which are present in the  
11 compounds of the invention either in the aromatic  
12 portion of the condensed ring system, or as a  
13 substituent of the aryl or heteroaryl group Y.  
14 Preferably a  $W_2$  group is present in the Y group, and  
15 a  $W_1$  group is also present in the aromatic portion of  
16 the condensed ring system. When the Z group is S  
17 (thioamides) a  $W_1$  or  $W_2$  group does not necessarily  
18 have to be present in the compounds of the invention  
19 in accordance with Formula 1, although preferably  
20 at least one of the  $W_1$  or  $W_2$  groups is nevertheless  
21 present. In the aryl or heteroaryl Y moiety in the  
22 compounds of Formula 1 and Formula 2 as well, the  $W_2$   
23 group is preferably located in the position adjacent  
24 to the B group; preferably the B group is in para  
25 position in the phenyl ring relative to the "amide"  
26 moiety, and therefore the  $W_2$  group is preferably in  
27 meta position relative to the amide moiety. Where  
28 there is a  $W_1$  group present in the aromatic portion  
29 of the condensed ring system of the compounds of  
30 Formula 1, it preferably occupies the 8 position of  
31 the chroman nucleus with the  $\text{Z}=\text{C}-\text{NH}-$  group occupying  
32 the 6 position. In tetrahydronaphthalene compounds  
33 of Formula 1, the  $\text{Z}=\text{C}-\text{NH}-$  group is preferably in the  
34 2-position, and the  $W_1$  group is preferably in the 4

1 position. However, when the  $W_1$  group is OH in  
2 compounds of Formula 1, then the OH is preferably in  
3 the 3 position of the tetrahydronaphthalene ring.

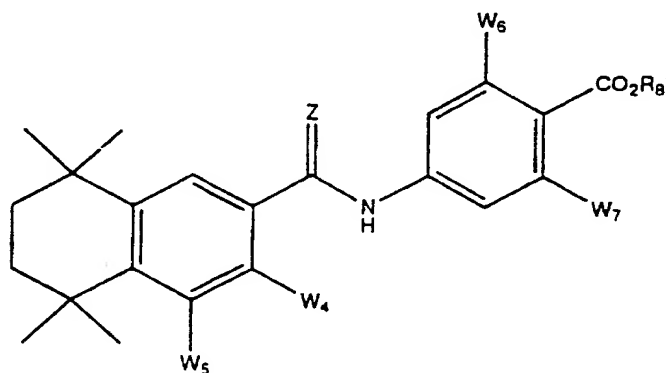
4 Preferred  $W_1$  and  $W_2$  groups are F,  $NO_2$ , Br, I,  
5  $CF_3$ ,  $ClN_3$ , and OH. The presence of one or two  
6 fluoro substituents in the Y group ( $W_2$ ) is especially  
7 preferred. When the Y group is phenyl, the fluoro  
8 substituents preferably are in the ortho and ortho'  
9 positions relative to the B group, which is  
10 preferably COOH or COOR<sub>1</sub>.

11 Referring now to the  $W_3$  group in Formula 2, this  
12 group is, generally speaking, also an electron  
13 withdrawing group or an alkyl group, more  
14 specifically preferred  $W_3$  groups are F,  $NO_2$ , Br, I,  
15  $CF_3$ ,  $N_3$ , and OH. Alternatively, in the phenyl or  
16 pyridyl ring (shown in Formula 2 as substituent  
17 " $(W_3)_p$ ")  $W_3$  is an alkyl group, preferably  
18 branch-chained alkyl, such as tertiary butyl, and  
19 preferably p is 2.

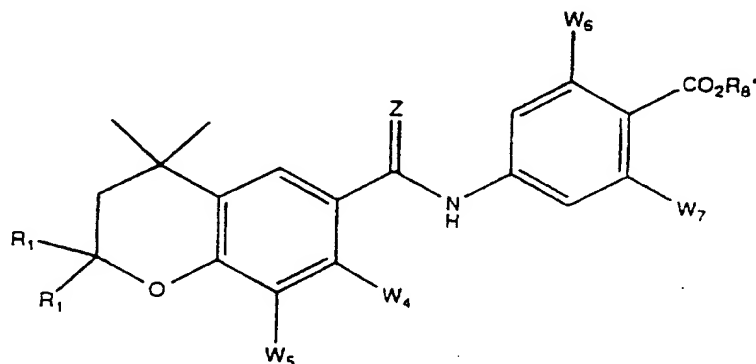
20 With reference to the symbol Y in Formula 1 and  
21 in Formula 2 as well, the preferred compounds used  
22 in the methods of the invention are those where Y is  
23 phenyl, pyridyl, 2-thiazolyl, thienyl, or furyl,  
24 more preferably phenyl. As far as substitutions on  
25 the Y (phenyl) and Y (pyridyl) groups are concerned,  
26 compounds are preferred where the phenyl group is  
27 1,4 (para) substituted by the L and B groups, and  
28 where the pyridine ring is 2,5 substituted by the L  
29 and B groups. (Substitution in the 2,5 positions in  
30 the "pyridine" nomenclature corresponds to  
31 substitution in the 6-position in the "nicotinic  
32 acid" nomenclature.) In the preferred compounds of  
33 the invention there is no optional  $R_1$  substituent  
34 (other than H) on the Y group.

The L group of Formula 1 and of Formula 2 is preferably  $-(C=Z)-NH-$ , and Z is preferably O. In other words, those carbamoyl or amide compounds are preferred in accordance with the present invention where the  $-NH-$  moiety is attached to the Y group.

The compounds which are presently most preferably used in the methods of treatment of the invention are shown below in Table 1 with reference to Formulas 3 and 4 and in Table 2 with reference to Formula 5.



Formula 3



Formula 4

## Formula 5

TABLE 1

Compound									
No.	Formula	R <sub>1</sub> '	W <sub>4</sub>	W <sub>5</sub>	Z	W <sub>6</sub>	W <sub>7</sub>	R <sub>8</sub> '	
1	3	--	H	H	O	F	H	Et	
2	3	--	H	H	O	F	H	H	
3	3	--	H	Br	O	F	H	Et	
4	3	--	H	Br	O	F	H	H	
5	3	--	OH	H	O	F	H	Et	
6	3	--	OH	H	O	F	H	H	
7	4	H	H	Br	O	F	H	Et	
8	4	H	H	Br	O	F	H	H	
9	4	CH <sub>3</sub>	H	Br	O	F	H	Et	
10	4	CH <sub>3</sub>	H	Br	O	F	H	H	
11	4	CH <sub>3</sub>	H	CF <sub>3</sub>	O	F	H	Et	
12	4	CH <sub>3</sub>	H	CF <sub>3</sub>	O	F	H	H	
13	4	CH <sub>3</sub>	H	N <sub>3</sub>	O	F	H	Et	
14	4	CH <sub>3</sub>	H	N <sub>3</sub>	O	F	H	H	
15	4	CH <sub>3</sub>	H	CF <sub>3</sub>	O	F	F	CH <sub>3</sub>	
16	4	CH <sub>3</sub>	H	CF <sub>3</sub>	O	F	F	H	
17	4	CH <sub>3</sub>	H	I	O	F	H	Et	
18	4	CH <sub>3</sub>	H	I	O	F	H	H	
19	4	CH <sub>3</sub>	H	CH <sub>3</sub>	O	F	H	Et	
20	4	CH <sub>3</sub>	H	CH <sub>3</sub>	O	F	H	H	
21	3	--	H	H	S	H	H	Et	
22	3	--	H	H	S	H	H	H	
23	3	--	H	H	S	F	H	Et	



1	24	3	--	H	H	S	F	H	H
2	25	3	--	H	Br	O	NO <sub>2</sub>	H	CH <sub>3</sub>
3	26	3	--	H	Br	O	NO <sub>2</sub>	H	H
4	27	4	CH <sub>3</sub>	H	H	O	F	H	Et
5	28	4	CH <sub>3</sub>	H	H	O	F	H	H
6	29	3	--	OH	Br	O	F	H	Et
7	30	3	--	OH	Br	O	F	H	H
8	31	3	--	OH	Br	O	F	F	Me
9	32	3	--	OH	Br	O	F	F	H
10	33	3	--	H	H	O	F	F	Me
11	34	3	--	H	H	O	F	F	H

12

13

Table 2

14	Compound #	X <sub>2</sub>	W <sub>8</sub>	W <sub>9</sub>	W <sub>10</sub>	R <sub>1</sub>
15	41	N	H	F	H	Et
16	42	N	H	F	H	H
17	43	N	H	H	H	Et
18	44	N	H	H	H	H
19	45	CH	H	F	H	Et
20	46	CH	H	F	H	H
21	47	CH	OH	F	H	Et
22	48	CH	OH	F	H	H
23	49	N	H	F	F	Me
24	50	N	H	F	F	H
25	51	CH	H	F	F	Me
26	52	CH	H	F	F	H
27	53	N	H	NO <sub>2</sub>	H	Me
28	54	N	H	NO <sub>2</sub>	H	H

29

30

Modes of Administration

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34

The RAR<sub>a</sub> specific or selective compounds used in the methods of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need

1 for site-specific treatment, quantity of drug to be  
2 administered, and numerous other considerations.

3 In the treatment of dermatoses, it will  
4 generally be preferred to administer the drug  
5 topically, though in certain cases such as treatment  
6 of severe cystic acne or psoriasis, oral  
7 administration may also be used. Any common topical  
8 formulation such as a solution, suspension, gel,  
9 ointment, or salve and the like may be used.  
10 Preparation of such topical formulations are well  
11 described in the art of pharmaceutical formulations  
12 as exemplified, for example, Remington's  
13 Pharmaceutical Science, Edition 17, Mack Publishing  
14 Company, Easton, Pennsylvania. For topical  
15 application, these compounds could also be  
16 administered as a powder or spray, particularly in  
17 aerosol form. If the drug is to be administered  
18 systemically, it may be confected as a powder, pill,  
19 tablet or the like or as a syrup or elixir suitable  
20 for oral administration. For intravenous or  
21 intraperitoneal administration, the compound will be  
22 prepared as a solution or suspension capable of  
23 being administered by injection. In certain cases,  
24 it may be useful to formulate these compounds by  
25 injection. In certain cases, it may be useful to  
26 formulate these compounds in suppository form or as  
27 extended release formulation for deposit under the  
28 skin or intramuscular injection.

29 Other medicaments can be added to such topical  
30 formulation for such secondary purposes as treating  
31 skin dryness; providing protection against light;  
32 other medications for treating dermatoses;  
33 medicaments for preventing infection, reducing  
34 irritation, inflammation and the like.

1 Treatment of dermatoses or any other indications  
2 known or discovered to be susceptible to treatment  
3 by retinoic acid-like compounds will be effected by  
4 administration of the therapeutically effective dose  
5 of one or more compounds of the instant invention.  
6 A therapeutic concentration will be that  
7 concentration which effects reduction of the  
8 particular condition, or retards its expansion. In  
9 certain instances, the compound potentially may be  
10 used in prophylactic manner to prevent onset of a  
11 particular condition.

12 A useful therapeutic or prophylactic  
13 concentration will vary from condition to condition  
14 and in certain instances may vary with the severity  
15 of the condition being treated and the patient's  
16 susceptibility to treatment. Accordingly, no single  
17 concentration will be uniformly useful, but will  
18 require modification depending on the  
19 particularities of the disease being treated. Such  
20 concentrations can be arrived at through routine  
21 experimentation. However, it is anticipated that in  
22 the treatment of, for example, acne, or similar  
23 dermatoses, that a formulation containing between  
24 0.01 and 1.0 milligrams per milliliter of formulation  
25 will constitute a therapeutically effective  
26 concentration for total application. If  
27 administered systemically, an amount between 0.01  
28 and 5 mg per kg per day of body weight would be  
29 expected to effect a therapeutic result in the  
30 treatment of many diseases for which these compounds  
31 are useful.

32 In the treatment of tumors a dose of  
33 approximately 0.5 to 5 mg per kg body weight per day  
34 is anticipated to constitute the therapeutic dose.

1 Alternatively, as is performed frequently in therapy  
2 of malignancies, a patient is provided an initial  
3 dose of 1 mg per kg body weight per day, and  
4 thereafter the dose is raised until a maximum  
5 tolerated dose is attained.

6 Assay of RAR<sub>α</sub> receptor selective biological activity  
7 and its significance in reduced side effects and  
8 toxicity

9 As it is noted in the introductory section of  
10 this application for patent two main types of  
11 retinoic acid receptors (RAR and RXR) exist in  
12 mammals (and other organisms). Within each type  
13 there are sub-types (RAR<sub>α</sub>, RAR<sub>β</sub>, RAR<sub>γ</sub>, RXR<sub>α</sub>, RXR<sub>β</sub> and  
14 RXR<sub>γ</sub>) the distribution of which is not uniform in the  
15 various tissues and organs of mammalian organisms.  
16 Selective binding of only one or two retinoid  
17 receptor subtypes within one retinoid receptor  
18 family can give rise to beneficial pharmacological  
19 properties because of the varying distribution of  
20 the sub-types in the several mammalian tissues or  
21 organs. For the above-summarized reasons, binding  
22 of any or all of the retinoid receptors, as well as  
23 specific or selective activity in a receptor family,  
24 or selective or specific activity in any one of the  
25 receptor subtypes, are all considered desirable  
26 pharmacological properties.

27 In light of the foregoing the prior art has  
28 developed assay procedures for testing the agonist  
29 like activity of compounds in the RAR<sub>α</sub>, RAR<sub>β</sub>, RAR<sub>γ</sub>,  
30 RXR<sub>α</sub>, RXR<sub>β</sub> and RXR<sub>γ</sub> receptor subtypes. For example,  
31 a chimeric receptor transactivation assay which  
32 tests for agonist-like activity in the RAR<sub>α</sub>, RAR<sub>β</sub>,  
33 RAR<sub>γ</sub>, and RXR<sub>α</sub> receptor subtypes, and which is based  
34 on work published by Feigner P. L. and Holm M.

1 (1989) Focus, 11 2 is described in detail in U.S.  
2 Patent No. 5,455,265. The specification of United  
3 States Patent No. 5,455,265 is expressly  
4 incorporated herein by reference.

5 A holoreceptor transactivation assay and a  
6 ligand binding assay which measure the ability of  
7 compounds to bind to the several retinoid receptor  
8 subtypes, respectively, are described in published  
9 PCT Application No. WO WO93/11755 (particularly on  
10 pages 30 - 33 and 37 - 41) published on June 24,  
11 1993, the specification of which is also  
12 incorporated herein by reference. A description of  
13 the ligand binding assay is also provided below.

#### 14 **BINDING ASSAY**

15 All binding assays were performed in a similar  
16 fashion. All six receptor types were derived from  
17 the expressed receptor type (RAR  $\alpha$ ,  $\beta$ ,  $\gamma$  and RXR  $\alpha$ ,  
18  $\beta$ ,  $\gamma$ ) expressed in Baculovirus. Stock solutions of  
19 all compounds were prepared as 10mM ethanol  
20 solutions and serial dilutions carried out into 1:1  
21 DMSO; ethanol. Assay buffers consisted of the  
22 following for all six receptor assays: 8% glycerol,  
23 120mM KCl, 8mM Tris, 5mM CHAPS 4mM DTT and 0.24mM  
24 PMSF, pH - 7.4@ room temperature.

25 All receptor binding assays were performed in  
26 the same manner. The final assay volume was 250 $\mu$ l  
27 and contained from 10-40 $\mu$ g of extract protein  
28 depending on receptor being assayed along with 5 nM  
29 of [ $^3$ H] all-trans retinoic acid or 10nM [ $^3$ H] 9-cis  
30 retinoic acid and varying concentrations of  
31 competing ligand at concentrations that ranged from  
32 0 -  $10^{-5}$  M. The assays were formatted for a 96 well  
33 minitube system. Incubations were carried out at  
34 4°C until equilibrium was achieved. Non-specific

1 binding was defined as that binding remaining in the  
2 presence of 1000nM of the appropriate unlabeled  
3 retinoic acid isomer. At the end of the incubation  
4 period, 50 $\mu$ l of 6.25% hydroxyapatite was added in  
5 the appropriate wash buffer. The wash buffer  
6 consisted of 100mM KCl, 10mM Tris and either 5mM  
7 CHAPS (RXR  $\alpha$ ,  $\beta$ ,  $\gamma$ ) or 0.5% Triton X-100 (RAR  $\alpha$ ,  $\beta$ ,  
8  $\gamma$ ). The mixture was vortexed and incubated for 10  
9 minutes at 4°C, centrifuged and the supernatant  
10 removed. The hydroxyapatite was washed three more  
11 times with the appropriate wash buffer. The  
12 receptor-ligand complex was adsorbed by the  
13 hydroxyapatite. The amount of receptor-ligand  
14 complex was determined by liquid scintillation  
15 counting of hydroxyapatite pellet.

16 After correcting for non-specific binding, IC<sub>50</sub>  
17 values were determined. The IC<sub>50</sub> value is defined as  
18 the concentration of competing ligand needed to  
19 reduce specific binding by 50%. The IC<sub>50</sub> value was  
20 determined graphically from a loglogit plot of the  
21 data. The K<sub>d</sub> values were determined by application  
22 of the Cheng-Prusoff equation to the IC<sub>50</sub> values, the  
23 labeled ligand concentration and the K<sub>d</sub> of the  
24 labeled ligand.

25 The results of ligand binding assay are expressed  
26 in K<sub>d</sub> numbers. (See Cheng et al. Biochemical  
27 Pharmacology Vol. 22 pp 3099-3108, expressly  
28 incorporated herein by reference.)

29 Table 3 shows the results of the ligand binding  
30 assay for certain exemplary compounds of the  
31 invention.

**TABLE 3**  
**Ligand Binding Assay**

Compound #	K <sub>d</sub> (nanomolar)					RXR $\alpha$	RXR $\beta$
	RAR $\alpha$	RAR $\beta$	RAR $\gamma$				
RXRF							
2	1.90	480.0	0.00	0.00		0.00	0.00
4	1.3	0.00	0.00	0.00		0.00	0.00
6	3.00	0.00	0.00	0.00		0.00	0.00
10	24.0	0.00	0.00	0.00		0.00	0.00
12	14.0	0.00	0.00	0.00		0.00	0.00
14	52.0	0.00	0.00	0.00		0.00	0.00
16	51.0	0.00	0.00	0.00		0.00	0.00
18	16.0	0.00	0.00	0.00		0.00	0.00
20	57.0	0.00	0.00	0.00		0.00	0.00
22	15	0.00	0.00	0.00		0.00	0.00
24	7.5	0.00	0.00	0.00		0.00	0.00
26	245.0	0.00	0.00	0.00		0.00	0.00
28	162.0	0.00	0.00	0.00		0.00	0.00
30	<3.00	0.00	0.00	0.00		0.00	0.00
32	2.30	0.00	0.00	0.00		0.00	0.00
34	9.00	0.00	0.00	0.00		0.00	0.00
42	14.00	0.00	0.00	0.00		0.00	0.00
44	19.00	0.00	0.00	0.00		0.00	0.00
46	26.0	0.00	0.00	0.00		0.00	0.00
48	77.0	0.00	0.00	0.00		0.00	0.00
50	62.0	0.00	0.00	0.00		0.00	0.00
52	87.0	0.00	0.00	0.00		0.00	0.00
54	94.0	0.00	0.00	0.00		0.00	0.00

TTNPB<sup>1</sup> 72 5 36

0.00 indicates value greater than 1000nM (nanomolar)

<sup>1</sup> TTNPB is a well known prior art retinoid (4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)propen-1-yl)benzoic acid, that is not RAR $\alpha$  selective.

1       As it can be seen from the foregoing data, the  
2 compounds used in accordance with the present  
3 invention specifically or selectively bind to RAR $\alpha$ .  
4 retinoid receptors. It has been discovered in  
5 accordance with the present invention that this  
6 unique type of selectivity allows the compounds to  
7 retain beneficial retinoid-like properties while  
8 reduces certain side effects and toxicity. More  
9 specifically, certain in vitro cell culture assays  
10 are described below, in which the ability of the RAR $\alpha$   
11 specific or selective compounds to significantly  
12 inhibit the growth of cancer cells is demonstrated.

### 13 **CANCER CELL LINE ASSAYS**

### 14 **MATERIALS AND METHODS**

#### 15 **Hormones**

16       All trans-retinoic acid (t-RA) (Sigma Chemicals  
17 Co., St. Louis, MO) was stored at -70°C. Prior to  
18 each experiment the compound was dissolved in 100%  
19 ethanol at 1 mM and diluted in culture medium  
20 immediately before use. All experiments were  
21 performed in subdued light. Controls were assayed  
22 using the same concentration of ethanol as present  
23 in the experimental plates and this concentration of  
24 diluent had no effect in either assay.

#### 25 **Cells and Cell Culture**

26       The cell lines, RPMI 8226, ME-180 and AML-193  
27 were obtained from the American Type Culture  
28 Collection (ATCC, Rockville, MD). RPMI 8226 is a  
29 human hematopoietic cell line obtained from the  
30 peripheral blood of a patient with multiple myeloma.  
31 The cells resemble the lymphoblastoid cells of other  
32 human lymphocyte cell lines and secrete  $\alpha$ -type light  
33 chains of immunoglobulin. RPMI-8226 cells are grown  
34 in RPMI medium (Gibco) supplemented with 10% fetal



1 bovine serum, glutamine and antibiotics. The cells  
2 were maintained as suspension cultures grown at 37°C  
3 in a humidified atmosphere of 5% CO<sub>2</sub> in air. The  
4 cells were diluted to a concentration of 1 x 10<sup>5</sup>/ml  
5 twice a week.

6 ME-180 is a human epidermoid carcinoma cell line  
7 derived from the cervix. The tumor was a highly  
8 invasive squamous cell carcinoma with irregular cell  
9 clusters and no significant keratinization. ME-180  
10 cells were grown and maintained in McCoy's 5a medium  
11 (Gibco) supplemented with 10% fetal bovine serum,  
12 glutamine and antibiotics. The cells were  
13 maintained as monolayer cultures grown at 37°C in a  
14 humidified atmosphere of 5% CO<sub>2</sub> in air. The cells  
15 were diluted to a concentration of 1 x 10<sup>5</sup>/ml twice a  
16 week.

17 AML-193 was established from the blast cells  
18 classified as M5 Acute Monocyte Leukemia. The  
19 growth factor, granulocyte colony-stimulation factor  
20 (GM-CSF) was required to establish this cell line  
21 and growth factors are necessary for its continuous  
22 proliferation in chemically defined medium. AML-193  
23 cells were grown and maintained in Iscove's modified  
24 Dulbecco's medium supplemented with 10% fetal bovine  
25 serum, glutamine and antibiotics with 5µg/ml insulin  
26 (Sigma Chemical Co.) and 2 ng/ml rh GM-CSF (R and D  
27 Systems). The cells were diluted to a concentration  
28 of 3 x 10<sup>5</sup>/ml twice a week.

#### 29 Incorporation of <sup>3</sup>H-Thymidine

30 The method used for determination of the  
31 incorporation of radiolabeled thymidine was adapted  
32 from the procedure described by Shrivastav et al.  
33 RPMI-8226 cells were plated in a 96 well round  
34 bottom microtiter plate (Costar) at a density of

1 1,000 cells/well. To appropriate wells, retinoid  
2 test compounds were added at the final  
3 concentrations indicated for a final volume of 150  
4  $\mu$ l/well. The plates were incubated for 96 hours at  
5 37°C in a humidified atmosphere of 5% CO<sub>2</sub> in air.  
6 Subsequently, 1  $\mu$ Ci of [5'-<sup>3</sup>H]-thymidine (Amersham,  
7 U.K. 43 Ci/mmol specific activity) in 25  $\mu$ l culture  
8 medium was added to each well and the cells were  
9 incubated for an additional 6 hours. The cultures  
10 were further processed as described below.

11 ME-180 wells, harvested by trypsinization were  
12 plated in a 96 well flat bottom microtiter plate  
13 (Costar) at a density of 2,000 cells/well. The  
14 cultures were treated as described above for RPMI  
15 8226 with the following exceptions. After  
16 incubation with thymidine the supernatant was  
17 carefully removed, and the cells were washed with a  
18 0.5 mM solution of thymidine in phosphate buffered  
19 saline. ME180 cells were briefly treated with 50 $\mu$ l  
20 of 2.5% trypsin to dislodge the cells from the  
21 plate.

22 AML-193 cells were plated in a 96 well round  
23 bottom microtiter plate (Costar) at a density of  
24 1,000 cells/well. To appropriate wells, retinoid  
25 test compounds were added at the final  
26 concentrations indicated for a final volume of 150  
27  $\mu$ l/well. The plates were incubated for 96 hours at  
28 37°C in a humidified atmosphere of 5% CO<sub>2</sub> in air.  
29 Subsequently, 1  $\mu$ Ci of [5'-<sup>3</sup>H]-thymidine (Amersham,  
30 U.K., 43 Ci/mmol specific activity) in 25  $\mu$ l culture  
31 medium was added to each well and the cells were  
32 incubated for an additional 6 hours.

33 The cell lines were then processed as follows:  
34 the cellular DNA was precipitated with 10%

1 trichloroacetic acid onto glass fiber filter mats  
2 using a SKATRON multi-well cell harvester (Skatron  
3 Instruments, Sterling VA). Radioactivity  
4 incorporated into DNA, as a direct measurement of  
5 cell growth, was measured by liquid scintillation  
6 counting. The numbers represent the mean  
7 disintegrations per minute of incorporated thymidine  
8 from triplicate wells  $\pm$  SEM.

9 The graph of Figure 1 of the appended drawings  
10 shows that in the above described RPMI 8226 cell  
11 (malignant myeloma) culture assay Compounds 4 and 12  
12 (two exemplary compounds used in accordance with  
13 this invention) inhibited the growth of these  
14 malignant cells, substantially as well as a  
15 comparison compound, all trans retinoic acid (ATRA).  
16 The graph of Figure 1 also demonstrates that whereas  
17 in a low concentration range ( $10^{-12}$  to approximately  
18  $10^{-9}$ ) all trans retinoic acid (ATRA) actually  
19 facilitates growth of these cells, the  $RAR_{\alpha}$  selective  
20 Compounds 4 and 12 of the present invention do not  
21 stimulate but rather already in this low  
22 concentrations inhibit the growth of these malignant  
23 cells.

24 The graph of Figure 2 shows that in the above  
25 described AML 193 (acute monocytic leukemia) cell  
26 culture assay Compounds 22 and 42 in accordance with  
27 this invention inhibited the growth of these  
28 malignant cells. Two other compounds for which data  
29 are also shown in this graph are designated AGN  
30 193090 and AGN 193459. (An AGN number is an  
31 arbitrary designation number used by the corporate  
32 assignee of the present invention.) The compounds  
33 AGN 193090 and AGN 193459 are not  $RAR_{\alpha}$  selective.  
34 These compounds respectively are

1 4-[(8-cyano-5,6-dihydro-5,5-dimethylnaphth-2-yl)ethy  
2 nyl]benzoic acid, and  
3 4-[(5,6-dihydro-5,5-dimethylnaphth-7(6H)-8-(1-2,2-di  
4 methylpropylidene)naphth-2-yl)ethynyl]benzoic acid,  
5 and their Kd values for RAR<sub>α</sub>, RAR<sub>β</sub> and RAR<sub>γ</sub> receptors  
6 are 109, 34, 77 and 6, 2, 7, respectively. The  
7 graph of Figure 2 demonstrates that the RAR<sub>α</sub>  
8 selective or specific compounds inhibit the  
9 malignant cell growth at low concentrations where  
10 the pan agonist AGN 193090 and AGN 193459 compounds  
11 do not inhibit but rather at these low  
12 concentrations even stimulate such cell growth.

13 Figure 3 is another graph showing the results of  
14 an AML-193 cell culture assay, where Compounds 4, 12  
15 and 18 in accordance with the present invention, and  
16 all trans retinoic acid (ATRA) were tested. The  
17 data show that the RAR<sub>α</sub> selective compounds reduce  
18 cell proliferation at low concentrations whereas  
19 ATRA at the same low concentration actually promotes  
20 cell proliferation.

21 In another line of assays the effect of the  
22 retinoid compounds is tested against cells obtained  
23 from solid tumors of patients. This EDR assay is  
24 described below as follows:

25 Freshly resected solid tumor biopsies were  
26 received within 24 hours of surgery. Species were  
27 processed for assay after retaining a portion of the  
28 tumor for paraffin embedding and histopathologic  
29 confirmation of specimen viability and tissue  
30 diagnosis. The remaining specimen was dissociated  
31 into small fragments using sterile scissors. The  
32 small tissue fragments were then exposed to  
33 collagenase and DNAase for 2 hours with mixing a CO<sub>2</sub>  
34 incubator in order to release the tumor cells from

1 the connective tissue stroma. The resulting cell  
2 suspension was washed, and cell counts determined  
3 from a cytopsin preparation. Tumor cells were  
4 resuspended at 40,000 cells per ml in 0.3% agarose  
5 in RMPI 1640 supplemented with 15% FCS, glutamine  
6 and antibiotics, and 0.5 ml were plated into each  
7 well of a 24 well plate over 0.5 ml layer of 0.5%  
8 agarose. These culture conditions prevent cell  
9 adherence, thereby allowing only transformed cells  
10 to proliferate. Additionally, the cells grow into  
11 three dimensional spheroids, recapitulating their in  
12 vivo morphology.

13 Retinoid drugs were added 24 hours after plating  
14 to insure specimen reequilibration to a growth  
15 environment after the rigors of transport and  
16 processing. Cells were grown for four days in the  
17 presence of drug, with <sup>3</sup>H-thymidine (5 uCi/ml) added  
18 48 hours prior to harvest to insure adequate  
19 labeling of proliferating cells. After the  
20 agarose-cell suspension was liquefied at 90°C, cells  
21 were harvested onto glass fiber filters, which were  
22 counted in 5 ml scintillation fluid using a Beckman  
23 6500 liquid scintillation counter.

24 Results are reported as fraction of untreated  
25 control cell proliferation. Treatment groups were  
26 performed in duplicate or triplicate, while the  
27 controls were performed in quadruplicate.

28 The graph of **Figure 4** shows the effect of  
29 **Compound 2** on ovarian tumors obtained from 4  
30 patients, and demonstrates that the compound  
31 inhibits this tumor cell proliferation in a  
32 concentration dependent manner.

33 It will be understood by those skilled in the  
34 art, that the ability of the RAR<sub>α</sub> selective compounds

1 to significantly inhibit growth of malignant cells  
2 in the above described assays is an indication that  
3 these compounds can be administered with beneficial  
4 effect to tumor bearing mammals (including humans)  
5 for the treatment of tumors, particularly acute  
6 monocytic leukemia, cervical carcinoma, myeloma,  
7 ovarian carcinomas and head and neck carcinomas.

8 It has also been discovered in accordance with  
9 the present invention that the proliferation of  
10 retinal pigment epithelium cells is inhibited by RAR<sub>α</sub>  
11 selective compounds. By way of background it is  
12 noted that after retinal detachment the retinal  
13 pigment epithelium (RPE) becomes dedifferentiated,  
14 proliferates and migrates into the subretinal space  
15 (Campochiaro et al., Invest. Ophthal & Vis. Sci.  
16 32:65-72 (1991)). Such processes therefore have an  
17 impact upon the success of retinal reattachment  
18 procedures. RAR agonists such as all-trans-retinoic  
19 acid (ATRA) exhibit an antiproliferative effect upon  
20 the growth rate of primary human RPE cultures  
21 (Campochiaro et al., *ibid*) and have been shown to  
22 decrease the incidence of retinal detachment after  
23 retinal reattachment surgery in human studies  
24 (Fekrat et al., Ophthalmology 102:412-418 (1994)).

25 The graph of **Figure 5** shows the concentration  
26 dependent inhibitory effect of all trans retinoic  
27 acid (ATRA) and of **Compound 42** on RPE proliferation  
28 in an assay procedure which is described below.

29 Analysis of primary RPE cultures

30 Primary cultures of human retinal pigment  
31 epithelium (RPE) were established from eyes as  
32 previously described, (Campochiaro et al., Invest.  
33 Ophthal & Vis. Sci. 32:65-72 (1991)). 5 X 10<sup>4</sup> Cells  
34 were plated in 16-mm wells of 24-well multiwell

1 plates in Dulbecco's modified Eagle's medium (DMEM  
2 Gibco) containing 10% fetal bovine serum (FBS).  
3 Cells were treated with ethanol alone (control),  
4 ATRA ( $10^{-10}$  to  $10^{-6}$  M) in ethanol, and **Compound 42**  
5 ( $10^{-10}$  to  $10^{-6}$  M) in ethanol. Cells were fed with  
6 fresh media containing the appropriate  
7 concentrations of these compounds every two days for  
8 a total of six days treatment. Cells were removed  
9 from the plates via treatment with trypsin and the  
10 number of cells were counted with an electronic cell  
11 counter. As it can be seen in **Figure 5** treatment of  
12 primary RPE cells with ATRA and with **Compound 42**  
13 both led to a dose dependent decrease in RPE cell  
14 proliferation.

15 The effect of topically administering to  
16 experimental hairless mice  $RAR_{\alpha}$  selective retinoid  
17 compounds in accordance with the present invention  
18 was also evaluated in a topical skin irritation  
19 assay, using the  $RAR_{\alpha}$  selective **Compound 18** of the  
20 invention. More particularly, skin irritation was  
21 measured on a semi-quantitative scale by the daily  
22 subjective evaluation of skin flaking and abrasions.  
23 A single number, the topical irritation score,  
24 summarizes the skin irritation induced in an animal  
25 during the course of an experiment. The topical  
26 irritation score is calculated as follows. The  
27 topical irritation score is the algebraic sum of a  
28 composite flaking score and a composite abrasion  
29 score. The composite scores range from 0-9 and 0-8  
30 for flaking and abrasions, respectively, and take  
31 into account the maximum severity, the time of  
32 onset, and the average severity of the flaking and  
33 abrasions observed.

34 The severity of flaking is scored on a 5-point

1 scale and the severity of abrasions is scored on a  
2 4-point scale, with higher scores reflecting greater  
3 severity. The maximum severity component of the  
4 composite scores would be the highest daily severity  
5 score assigned to a given animal during the course  
6 of observation.

7 For the time of onset component of the composite  
8 score, a score ranging from 0 to 4 is assigned as  
9 follows:

10

11	Time to Appearance of	
12	Flaking or Abrasions of	
13	Severity 2 or greater	
14	(days)	Time of Onset Score
15	<hr/>	<hr/>
16	8	0
17	6-7	1
18	5	2
19	3-4	3
20	1-2	4

21

22 The average severity component of the composite  
23 score is the sum of the daily flaking or abrasion  
24 scores divided by the number of observation days.  
25 The first day of treatment is not counted, since the  
26 drug compound has not had an opportunity to take  
27 effect at the time of first treatment.

28 To calculate the composite flaking and abrasion  
29 scores, the average severity and time of onset  
30 scores are summed and divided by 2. The result is  
31 added to the maximal severity score. The composite  
32 flaking and abrasion scores are then summed to give  
33 the overall topical irritation score. Each animal  
34 receives a topical irritation score, and the values



are expressed as the mean  $\pm$  SD of the individual scores of a group of animals. Values are rounded to the nearest integer.

Thus, female hairless mice [Crl:SKH1-hrBR] (8-12 weeks old, n=4) were treated topically for 5 consecutive days with **Compound 18** in doses expressed in nanomol/25 g, which is particularly given in **Table 4**. Treatments are applied to the dorsal skin in a total volume of 4 ml/kg (-0.1 ml). Mice were observed daily and scored for flaking and abrasions up to and including 3 days after the last treatment, i.e., day 8.

**Table 4**

**Eight Day Topical Assay in Hairless Mice  
of Compound 18**

Dose	Mortality	Body Weight	Flaking	Abrasion	
Composite					
(out of 4)	% gain or	Score	Score	Score	
	(loss)				
100	0	8 $\pm$ 7	0	1	1 $\pm$ 1
1000	0	4 $\pm$ 1	1	1	2 $\pm$ 0
<b>of TTNPB</b>					
0.9	0	5 $\pm$ 2	5	3	8 $\pm$ 2
2.7	0	(4 $\pm$ 3)	6	3	9 $\pm$ 2
9	0	(11 $\pm$ 3)	7	5	11 $\pm$ 2

These data show that the RAR <sub>$\alpha$</sub>  selective compound causes virtually no skin irritation and no weight

1 loss up to 1000 nmol/25g in the test model. For  
2 comparison it should be noted that the well known  
3 prior art retinoid compound  
4 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnapht  
5 halen-2-yl)propen-1-yl)benzoic acid (TTNPB), which  
6 is not RAR<sub>α</sub> selective, causes much more serious skin  
7 irritation in the above-noted test, as is shown in  
8 the foregoing table.

9 Another important advantage of administering  
10 RAR<sub>α</sub> selective retinoid compounds to a mammal lies in  
11 the significantly reduced teratogenic potency of the  
12 RAR<sub>α</sub> selective compounds compared to many other  
13 retinoids, as measured by a **chondrogenesis**  
14 **suppression bioassay**. This assay is performed as  
15 follows:

16 High-density "spot" cultures of limb bud  
17 mesenchymal cells are used to compare the ability of  
18 various concentrations of test drugs to suppress  
19 chondrogenic differentiation as a bioassay.  
20 Forelimb buds of mouse embryos on day 12 of  
21 gestation ( $54 \pm 2$  somites) are dissociated in a  
22 trypsin-EDTA solution, and the resultant single-cell  
23 suspension is plated as 20- $\mu$ l spots (200,000  
24 cells/spot) on plastic culture dishes. Retinoid  
25 concentrations ranging from 0.3 ng/ml to 3  $\mu$ g/ml (1  
26 nM-10  $\mu$ M) are added to the culture medium (Eagle's  
27 MEM + 10% fetal bovine serum, GIBCO) 24 hours after  
28 initial plating. Control cultures receive only the  
29 vehicle (ethanol, concentration  $\leq 1\%$  by vol);  
30 Retinoic acid is used as a positive control in  
31 another set of cultures.

32 The cultures are terminated 96 hours after  
33 plating, at which time the medium is removed and the  
34 cells are fixed for 1 hour in 10% formalin

1 containing 0.5% cetylpyridinium chloride. The  
2 cultures are rinsed in acetic acid and stained for 1  
3 hour in 0.5% Alcian blue solution at pH 1.0,  
4 differentiated in 3% acetic acid, and then  
5 dehydrated in ethanol and scored for chondrogenesis  
6 under the microscope. An absence or reduction in  
7 the number of cartilage nodules in stained cultures  
8 as compared with control cultures is taken as a  
9 measure of suppression of chondrogenesis. The  
10 number of cartilage nodules stained in the whole  
11 spot, mean number of nodules, and standard  
12 deviations are calculated for four replicate  
13 cultures per treatment. The median concentration  
14 causing a 50% inhibition of chondrogenesis compared  
15 with controls ( $IC_{50}$ ) is calculated by logarithmic  
16 curve fitting of the dose-response data. The  $IC_{50}$   
17 values are expressed in nanogram per milliliter  
18 (ng/ml) units. An  $IC_{50}$  value of greater  
19 concentration in this assay signifies lesser  
20 teratogenicity. **Table 5** indicates the results  
21 obtained in this assay for **Compounds 10, 18, and 42**  
22 in accordance with the present invention, as well as  
23 for comparison with all trans retinoic acid (ATRA)  
24 and 4-(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetra-  
25 methyl-naphthalen-2-yl)propen-1-yl)benzoic acid  
26 (TTNPB).

**Table 5**

Compound	$IC_{50}$ (ng/ml)
10	250
18	220
42	65
ATRA	55
TTNPB	0.01

1       As it can be seen the compounds used in  
2 accordance with the present invention are less  
3 teratogenic than all trans retinoic acid and  
4 significantly (of the  $10^4$  order of magnitude) less  
5 teratogenic than the prior art TTNPB compound.

6       Weight loss or gain that experimental animals  
7 experience upon administration of retinoid compounds  
8 is another test of the drug's toxicity, with  
9 significant weight loss at relatively low doses  
10 indicating a significant toxic side effect of the  
11 retinoid. In one experiment, groups of 5 rats were  
12 treated with varying doses (administered in corn  
13 oil) of a test retinoid for 3 days. The rats were  
14 euthanized 24 hours after the last dose. The graph  
15 of **Figure 6** shows the average weight of each group  
16 of rats treated with a daily dose of 10, 30, and 90  
17  $\mu\text{mol/kg/day}$  of **Compound 42**, as well as the average  
18 weight of a group of control rats which were not  
19 given the retinoid. As it can be seen, the RAR $_{\alpha}$   
20 selective **Compound 42** caused virtually no weight  
21 loss, as compared to the control, except in a very  
22 high dose (90  $\mu\text{mol/kg/day}$ ). The graph of **Figure 7**  
23 shows the weight of the rats on the fourth day (24  
24 hours after last administration of retinoid) in a  
25 similar test with varying doses of **Compound 18**, with  
26 a zero dose indicating the control. As it can be  
27 seen, this RAR $_{\alpha}$  selective retinoid caused virtually  
28 no weight loss even in the high dose of 90  
29  $\mu\text{mol/kg/day}$ . It is noteworthy that in similar tests  
30 TTNPB, which binds to all three RAR receptor  
31 subtypes (see **Table 3**) causes very significant  
32 weight loss. In this experiment involving the rats  
33 treated with **Compound 42**, significant mucocutaneous  
34 toxicity was not observed.

1           In another experiment three-week old male  
2 Hartley guinea pigs were implanted intraperitoneally  
3 with osmotic pumps containing 20 % DMSO/80  
4 polyethylene glycol (vehicle) or **Compound 42** at  
5 concentrations of 4.4, 13.3 or 40 mg/ml in vehicle.  
6 Based on the initial body weights and known pumping  
7 rate, approximate doses of 0, 2, 6, and 18 mg/kg/day  
8 doses of **Compound 42** are estimated. Body weights  
9 and clinical observations were recorded at least  
10 every other day for 14 days post-implantation. The  
11 guinea pigs were euthanized after 14 days, and the  
12 pumps were examined for possible failure. The graph  
13 of **Figure 8** shows the weight of the animals involved  
14 in this experiment over the course of 15 days. As  
15 it can be seen from the graph, the lower and middle  
16 doses of the RAR<sub>α</sub> selective retinoid compound  
17 (**Compound 42**) caused no, or only statistically  
18 insignificant depression of weight gain, relative to  
19 the control animals. Significant depression of  
20 weight gain was observed only in the high dose  
21 (18mg/kg/day) of **Compound 42**. Importantly, no signs  
22 of mucocutaneous toxicity were observed at any dose  
23 of **Compound 42** in this experiment. The foregoing,  
24 markedly reduced mucocutaneous toxicity observed  
25 when animals are treated with RAR<sub>α</sub> selective  
26 compounds in accordance with the present invention,  
27 is a significant advantage, because mucocutaneous  
28 toxicity is the major and most irksome retinoid side  
29 effect or toxicity in human patients.

30 Synthetic Methods for Preparing the Preferred  
31 Examples of RAR<sub>α</sub> Selective Compounds of the Invention

32           General structure of the compounds which are  
33 preferably used in the methods of treatment of the  
34 present invention are shown above in **Formula 1** and

1 **Formula 2.** These compounds can be made by the  
2 synthetic chemical pathways illustrated here. The  
3 synthetic chemist will readily appreciate that the  
4 conditions set out here are specific embodiments  
5 which can be generalized to any and all of the  
6 compounds represented by these formulas.

7 Generally speaking the process of preparing  
8 compounds preferably used in the methods of the  
9 invention in accordance with **Formula 1** involves the  
10 formation of an amide by the reaction of a compound  
11 of the general **Formula 6** with a compound of general  
12 **Formula 7**, or by the reaction of a compound of  
13 general **Formula 6a** with a compound of general  
14 **Formula 7a**. Similarly, the process of preparing  
15 compounds in accordance with **Formula 2** involves the  
16 formation of an amide by the reaction of a compound  
17 of the general **Formula 8** with a compound of general  
18 **Formula 7**, or by the reaction of a compound of  
19 general **Formula 8a** with a compound of general  
20 **Formula 7a**.

21 A compound of **Formula 6** is an acid or an  
22 "activated form" of a carboxylic acid attached to  
23 the aromatic portion of a tetrahydronaphthalene, ( $X_1$   
24 =  $[C(R_1)_2]_n$  and  $n$  is 1), dihydroindene ( $[C(R_1)_2]_n$  where  
25  $n$  is 0) or chroman ( $X_1$  is 0) nucleus. The carboxylic  
26 acid, or its "activated form" is attached to the 2  
27 or 3 position of the tetrahydronaphthalene, and to  
28 the 6 or 7 position of the chroman moieties. In the  
29 compounds preferably used in accordance with the  
30 invention the attachment is to the 2 position of  
31 tetrahydronaphthalene and to the 6 position of  
32 chroman.

33 The term "activated form" of the carboxylic acid  
34 should be understood in this regard as such

1 derivative of the carboxylic acid which is capable  
2 of forming an amide when reacted with a primary  
3 amine of **Formula 7**. In case of the "reverse amides"  
4 the activated form of a carboxylic acid is a  
5 derivative (**Formula 7a**) that is capable of forming  
6 an amide when reacted with a primary amine of  
7 **Formula 6a**. This, generally speaking, means such  
8 derivatives of a carboxylic acid which are normally  
9 known and used in the art to form amide linkages  
10 with an amine. Examples of suitable forms or  
11 derivatives for this purpose are acid chlorides,  
12 acid bromides, and esters of the carboxylic acid,  
13 particularly active esters, where the alcohol moiety  
14 of the ester forms a good leaving group. Presently  
15 most preferred as reagents in accordance with  
16 **Formula 6** (or **Formula 7a**) are acid chlorides ( $X$ , is  
17  $Cl$ ). The acid chlorides of **Formula 6** (or of **Formula**  
18 **7a**) can be prepared by traditional methods from the  
19 corresponding esters ( $X$ , is for example ethyl) by  
20 hydrolysis and treatment with thionyl chloride  
21 ( $SO_2Cl$ ). The acid chlorides of **Formula 6** (or of  
22 **Formula 7a**) can also be prepared by direct treatment  
23 of the carboxylic acids with thionyl chloride, where  
24 the carboxylic acid, rather than an ester thereof is  
25 available commercially or by a known synthetic  
26 procedure. The acid chlorides of **Formula 6** (or of  
27 **Formula 7a**) are typically reacted with the amine of  
28 **Formula 7** (or amine of **Formula 6a**) in an inert  
29 solvent, such as methylene chloride, in the presence  
30 of an acid acceptor, such as pyridine.

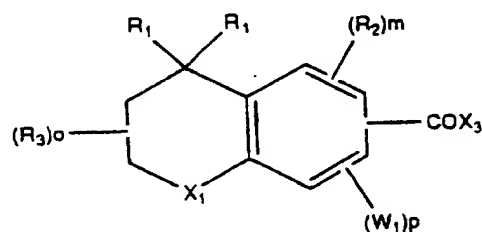
31 The carboxylic acids themselves in accordance  
32 with **Formula 6** (or **Formula 7a**) are also suitable for  
33 amide formation when reacted with an amine, a  
34 catalyst (4-dimethylaminopyridine) in the presence

1 of a dehydrating agent, such as  
2 dicyclohexylcarbodiimide (DCC) or more preferably  
3 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
4 hydrochloride (EDC).

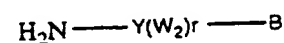
5 The carboxylic acids or the corresponding esters  
6 of **Formula 6**, are generally speaking, prepared as  
7 described in the chemical scientific or patent  
8 literature and the literature procedures for their  
9 preparation may be modified, if necessary, by such  
10 chemical reactions or processes which per se are  
11 known in the art. For example, generally speaking,  
12 2,2, 4,4 and/or 2,2,4,4-substituted chroman  
13 6-carboxylic acids and chroman 7-carboxylic acids  
14 are available in accordance with the teachings of  
15 United States Patent Nos. 5,006,550, 5,314,159,  
16 5,324,744, and 5,348,975, the specifications of  
17 which are expressly incorporated herein by  
18 reference. 5,6,7,8-Tetrahydronaphthalene-2-  
19 carboxylic acids are, generally speaking, available  
20 in accordance with the teachings of United States  
21 Patent No. 5,130,335, the specifications of which is  
22 expressly incorporated herein by reference.

23 The foregoing general description of the  
24 reactions which lead to formation of the amides of  
25 **Formula 1** is also, generally speaking, applicable to  
26 the formation of the amides of **Formula 2**. The  
27 reagents which are used in accordance with the  
28 general principles mentioned above for the formation  
29 of amide compounds of **Formua 2** are: activated forms  
30 of a carboxylic acids shown in **Formula 8** and in  
31 **Formula 7a**, and the amines of **Formula 7** and of  
32 **Formula 8a**.

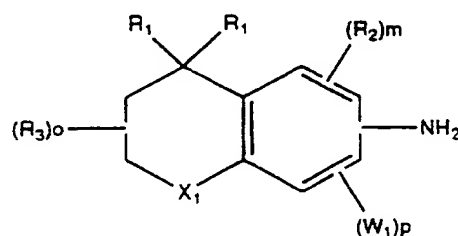




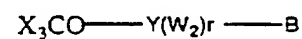
Formula 6



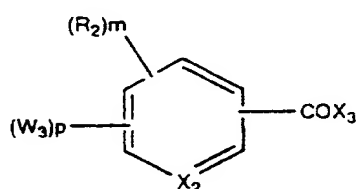
Formula 7



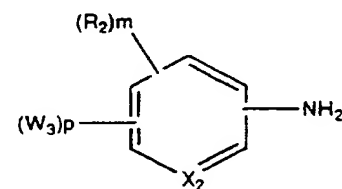
Formula 6a



Formula 7a



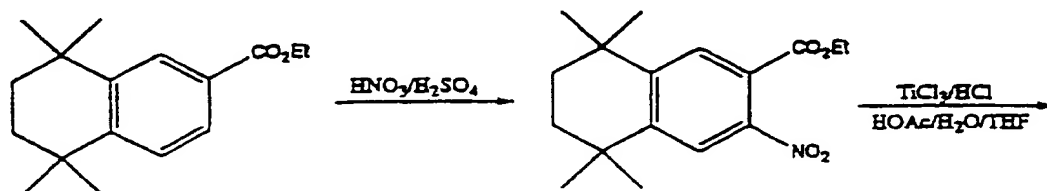
Formula 8



Formula 8a

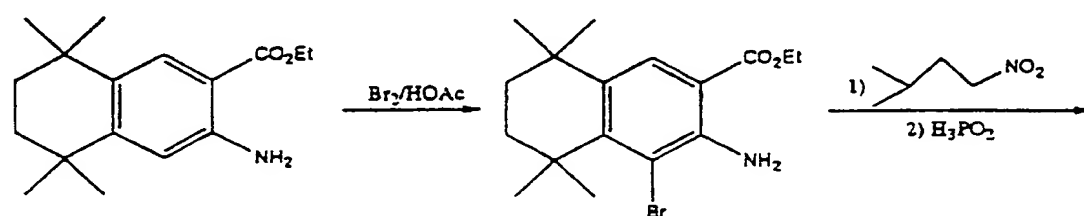
The carboxylic acids or the corresponding esters of **Formula 8**, are generally speaking, prepared as described in the chemical scientific or patent literature and the literature procedures for their preparation may be modified, if necessary, by such chemical reactions or processes which per se are known in the art.

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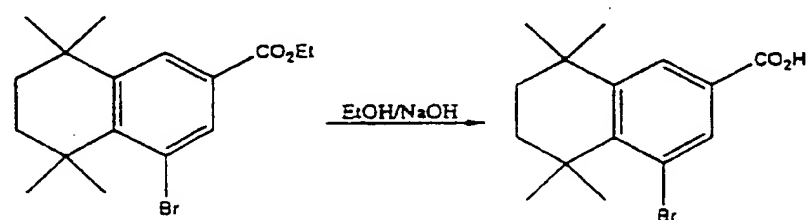
Compound A

Compound B



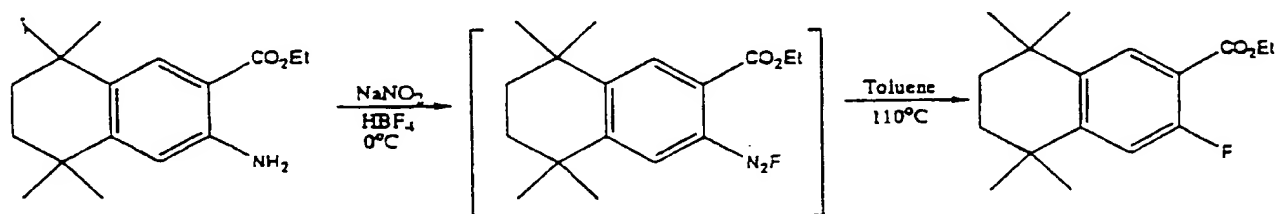
Compound C

Compound D



Compound E

Compound F

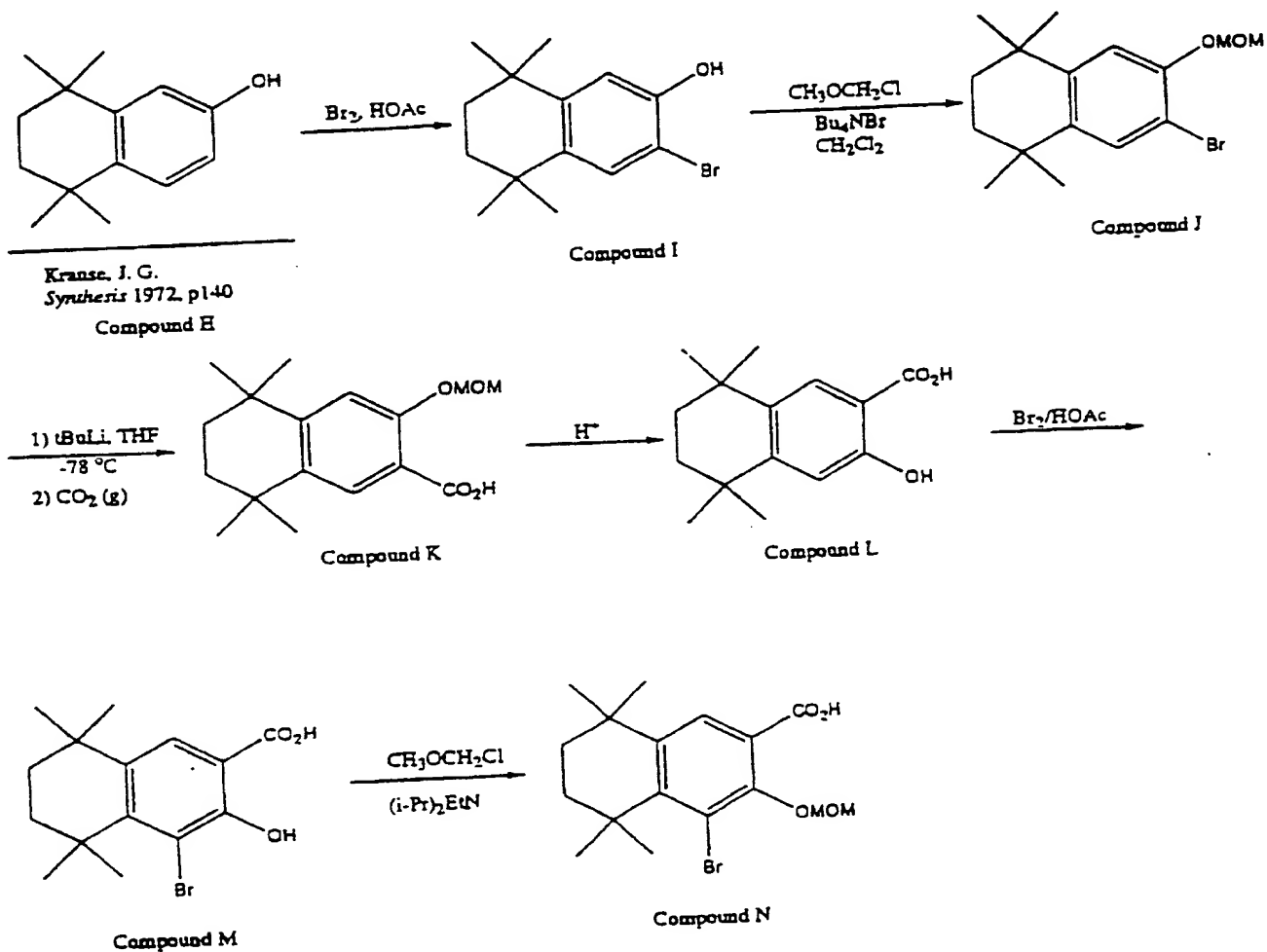


Compound C

Compound G

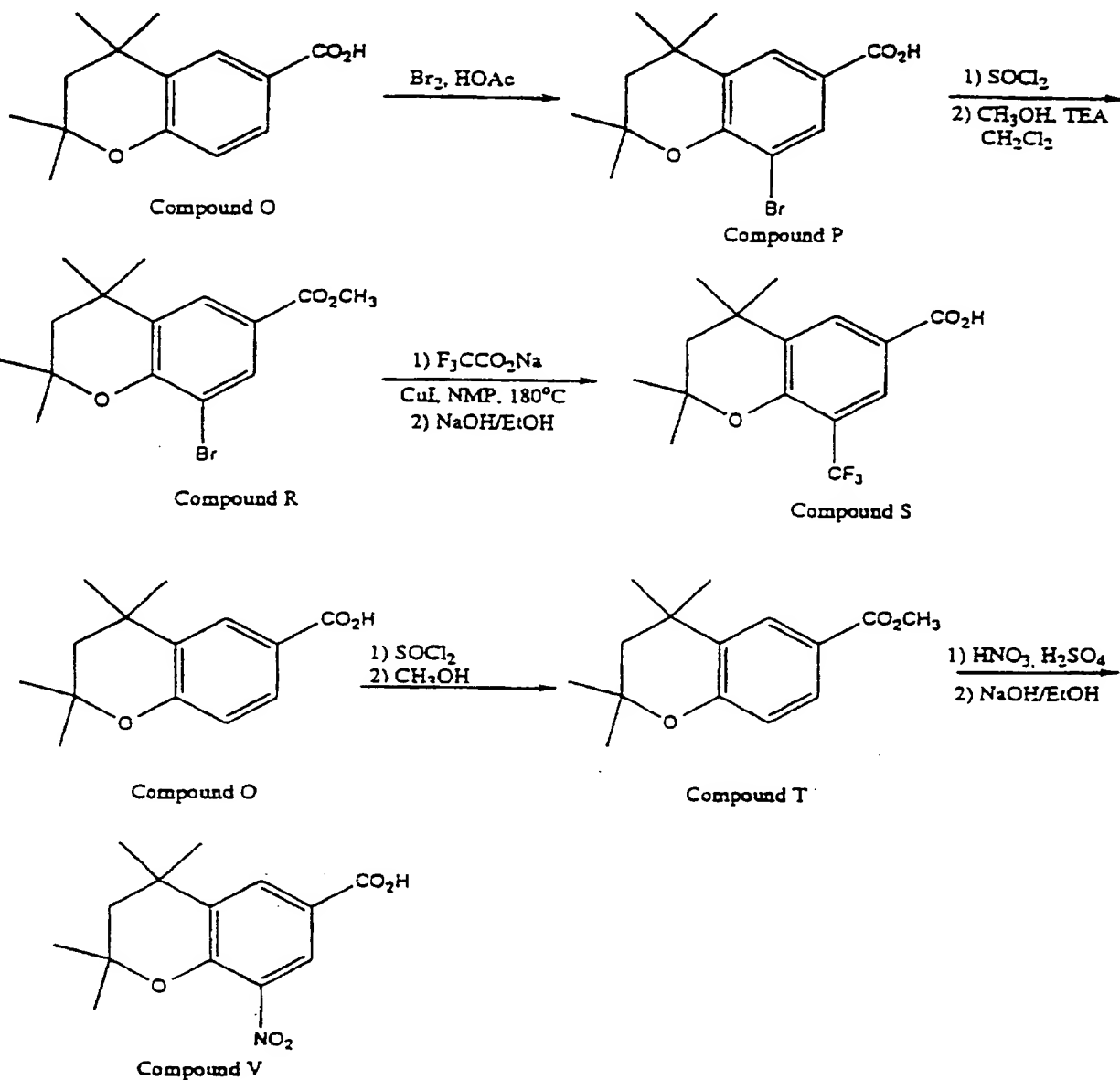
Reaction Scheme 1

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Reaction Scheme 2

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Reaction Scheme 2 (continued)

1        **Reaction Schemes 1 and 2** provide examples for  
2 the synthesis of derivatives of 5,6,7,8-tetrahydro-  
3 5,5,8,8-tetramethyl-naphthalene-2-carboxylic acid,  
4 which are within the scope of **Formula 6** and which  
5 are reacted with an amine of **Formula 7** to provide  
6 (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-  
7 2-yl)carbamoyl derivatives within the scope of  
8 **Formula 1**. Thus, as is shown in **Reaction Scheme 1**,  
9 ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
10 naphthalene-2-carboxylate (**Compound A**) is nitrated  
11 to provide the corresponding 3-nitro compound  
12 (**Compound B**). The nitro group of **Compound B** is  
13 reduced to provide the corresponding 3-amino  
14 compound (**Compound C**) which is described in the  
15 publication Lehmann et al. Cancer Research, 1991,  
16 51, 4804. Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-  
17 methyl-3-amino-naphthalene-2-carboxylate (**Compound**  
18 **C**) is brominated to yield the corresponding 4-bromo  
19 derivative (**Compound D**), which is converted by  
20 treatment with isoamylnitrite and reduction with  
21  $H_3PO_2$ , to ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetra-  
22 methyl- 4-bromonaphthalene-2-carboxylate (**Compound**  
23 **E**). Saponification of **Compound E** yields  
24 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth  
25 alene-2-carboxylic acid (**Compound F**) which is used  
26 as a reagent in accordance with **Formula 6**. Ethyl  
27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth  
28 alene-2-carboxylate (**Compound C**) is also diazotized  
29 and reacted with  $HBF_4$  to provide ethyl  
30 5,6,7,8-tetrahydro-5,5,8,8-tetra-methyl-3-fluoronaph  
31 thalene-2-carboxylate (**Compound G**) which serves  
32 either per se or after saponification as a reagent  
33 in accordance with **Formula 6**.

34        5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-

1 hydroxynaphthalene (Compound H, available in  
2 accordance with the publication Krause Synthesis  
3 1972 140), is the starting material in the example  
4 shown in Reaction Scheme 2. Compound H is  
5 brominated to provide the corresponding 3-bromo  
6 compound (Compound I) which is thereafter protected  
7 in the hydroxyl function by treatment with  
8 methoxymethyl chloride (MOMCl) to yield  
9 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-  
10 hoxy-2-bromonaphthalene (Compound J). Compound J is  
11 reacted with t-butyllithium and carbon dioxide to  
12 provide the corresponding carboxylic acid (Compound  
13 K) from which the methoxymethyl protecting group is  
14 removed by acid to give  
15 5,6,7,8-tetrahydro-5,5,8,8-tetra-  
16 methyl-2-hydroxynaphthalene-3-carboxylic acid  
17 (Compound L). Compound L is brominated to yield  
18 5,6,7,8-tetrahy-  
19 dro-5,5,8,8-tetramethyl-1-bromo-2-hydroxynaphthalene  
20 -3-carboxylic acid (Compound M). Compound L and  
21 Compound M serve as reagents in accordance with  
22 Formula 6. The hydroxy group of Compound M is  
23 protected for further transformations with  
24 methoxymethyl chloride (MOMCl) in the presence of  
25 base, yielding 5,6,7,8-tetrahydro-5,5,8,8-  
26 tetramethyl-1-bromo-2-methoxymethoxynaphthalene-3-ca  
27 rboxylic acid (Compound N).

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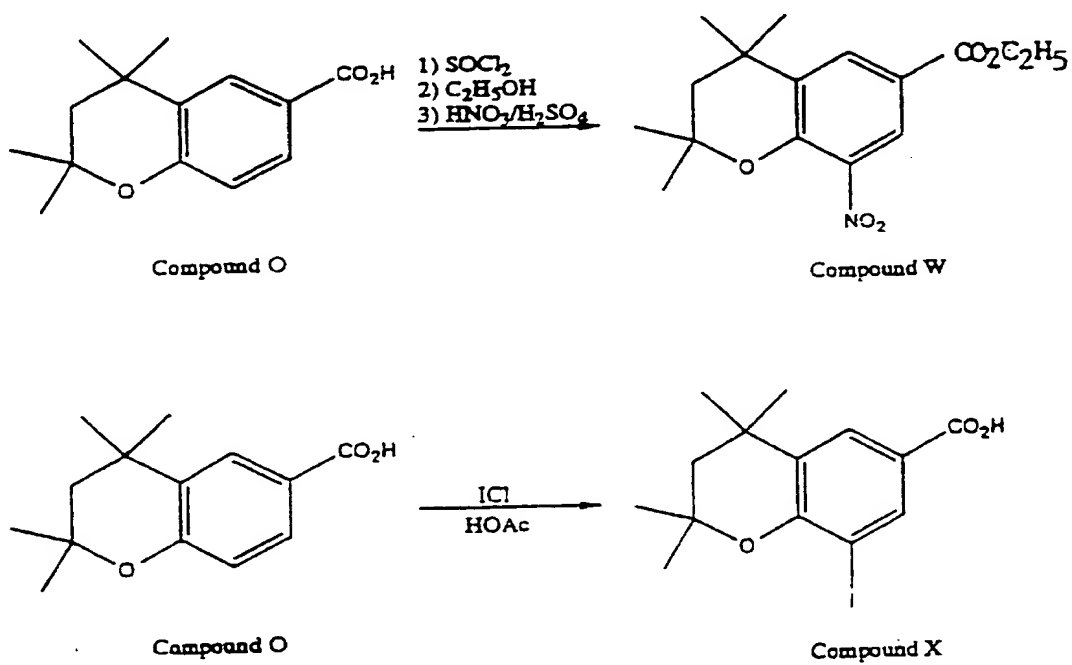
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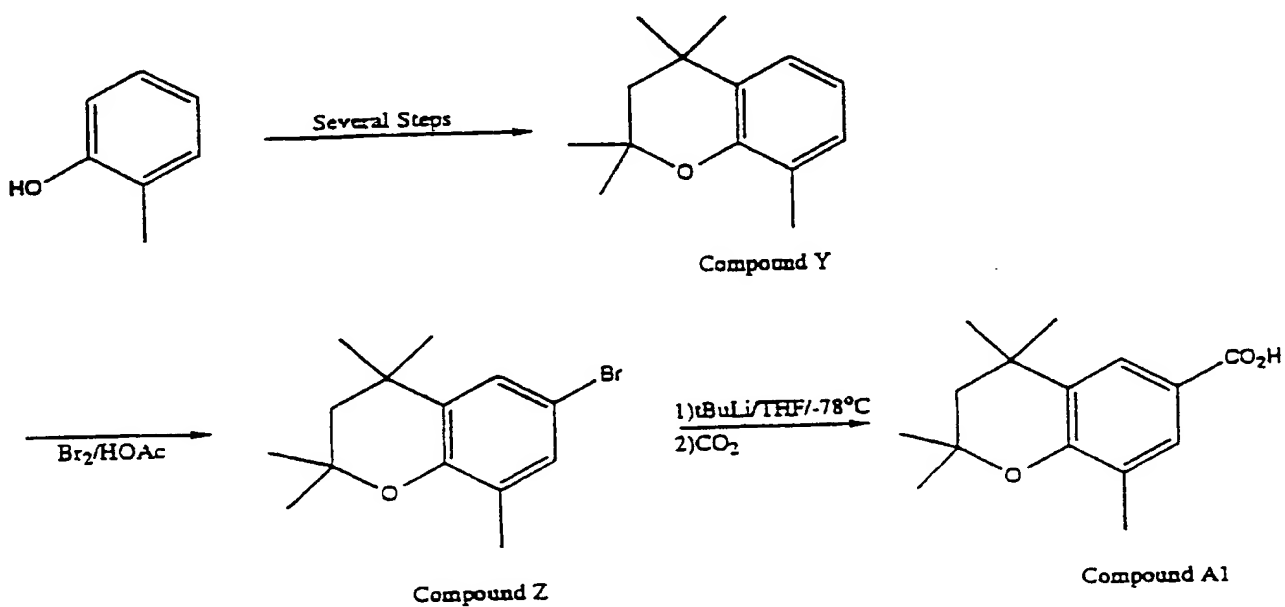
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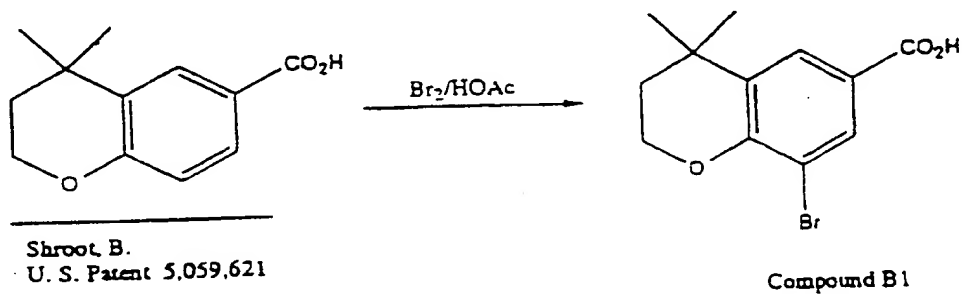
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Reaction Scheme 3



## Reaction Scheme 4



## Reaction Scheme 5



1        **Reaction Schemes 3, 4 and 5** provide examples for  
2 the synthesis of derivatives of 2,2,4,4 and  
3 4,4-substituted chroman-6-carboxylic acids which can  
4 serve as reagents in accordance with **Formula 6** for  
5 the synthesis of the carbamoyl (amide) compounds  
6 within the scope of the present invention. Thus,  
7 referring now to **Reaction Scheme 3**,  
8 2,2,4,4-tetramethylchroman-6-carboxylic acid  
9 (**Compound O**, see U. S. Patent No. 5,006,550) is  
10 brominated with bromine in acetic acid to yield the  
11 corresponding 8-bromo derivative (**Compound P**).  
12 **Compound P** is converted to the acid chloride by  
13 treatment with thionyl chloride, and the resulting  
14 acid chloride is suitable for reaction with an amine  
15 of **Formula 3** to provide the carbamoyl (amide)  
16 compounds of the invention. The acid chloride is  
17 also reacted with an alcohol (methanol) in the  
18 presence of base to yield the corresponding ester,  
19 methyl 2,2,4,4-tetramethyl-8-bromochroman-6-  
20 carboxylate (**Compound R**). The bromo function of  
21 **Compound R** is converted to a trifluoromethyl  
22 function by treatment with sodium trifluoroacetate  
23 in the presence of cuprous iodide catalyst and  
24 1-methyl-2-pyrrolidinone (NMP), and the carboxylate  
25 ester group is saponified to yield  
26 2,2,4,4-tetramethyl-8-trifluoromethylchroman-6-carbo-  
27 xylic acid (**Compound S**). **Compound S** is within the  
28 scope of **Formula 6** and is suitable per se or as the  
29 acid chloride or in other "activated" form to react  
30 with the amines of **Formula 7** to yield the carbamoyl  
31 (amide) compounds of the invention.  
32 2,2,4,4-Tetramethylchroman-6-carboxylic acid  
33 (**Compound O**) is also converted to the methyl ester  
34 (**Compound T**) which is then nitrated to yield

1 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylic acid  
2 (Compound V), still another reagent within the scope  
3 of Formula 6. Moreover, in the example further  
4 shown in Reaction Scheme 3,  
5 2,2,4,4-tetramethylchroman-6-carboxylic acid  
6 (Compound O) is converted to the ethyl ester and  
7 nitrated thereafter to yield ethyl  
8 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylate  
9 (Compound W). Still further, Compound O is reacted  
10 with ICl to yield 2,2,4,4-tetramethyl-8-iodochroman-  
11 6-carboxylic acid (Compound X).

12 In accordance with the example shown in Reaction  
13 Scheme 4, 2-methylphenol is subjected to a series of  
14 reactions in accordance with the teachings of United  
15 States Patent No. 5,045,551 (incorporated herein by  
16 reference) to yield 2,2,4,4,8-pentamethylchroman  
17 (Compound Y). Compound Y is brominated with bromine  
18 in acetic acid to give 2,2,4,4,8-pentamethyl-6-  
19 bromochroman (Compound Z) which is reacted with  
20 t-butyl lithium and thereafter with carbon dioxide  
21 to give 2,2,4,4,8-pentamethylchroman-6-carboxylic  
22 acid (Compound A<sub>1</sub>).

23 Reaction Scheme 5 illustrates the synthesis of  
24 4,4-dimethyl-8-bromochroman-6-carboxylic acid  
25 (Compound B<sub>1</sub>) by bromination of  
26 4,4,-dimethyl-chroman-6-carboxylic acid which is  
27 available in accordance with the teachings of United  
28 States Patent No. 5,059,621, the specification of  
29 which is incorporated herein by reference.  
30 2,2,4,4,8-Pentamethylchroman-6-carboxylic acid  
31 (Compound A<sub>1</sub>) and 4,4,-dimethyl-8-bromochroman-  
32 6-carboxylic acid (Compound B<sub>1</sub>) serve as reagents,  
33 either per se, or as the corresponding acid  
34 chlorides (or other "activated form), in accordance

1 with **Formula 6** for the synthesis of the carbamoyl  
2 (amide) compounds of the present invention.

3 Referring back now to the reaction between the  
4 reagent of **Formula 6** with an amine compound of  
5 **Formula 7** it is noted that the amine compounds are,  
6 generally speaking, available in accordance with the  
7 state-of-the-art. as described in the scientific and  
8 patent literature. More specifically, the amine  
9 compounds of **Formula 7** can be prepared as described  
10 in the scientific and patent literature, or from  
11 known compounds of the literature, by such chemical  
12 reactions or transformations which are within the  
13 skill of the practicing organic chemist. **Reaction**  
14 **Scheme 6** illustrates examples for the preparation of  
15 amine compounds of **Formula 7** (where Y is phenyl)  
16 from commercially available starting materials  
17 (Aldrich Chemical Company, or Research Plus, Inc.).  
18 The illustrated compounds of **Formula 7** are used for  
19 the synthesis of several preferred compounds used in  
20 the methods of the invention.

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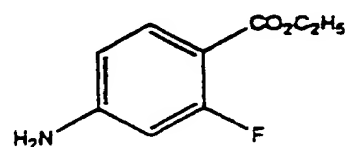
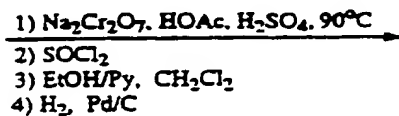
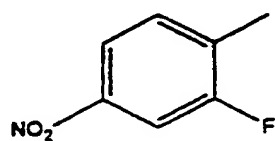
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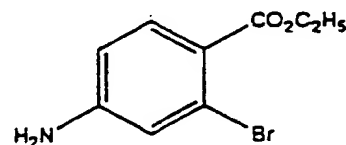
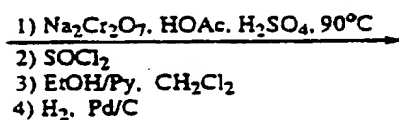
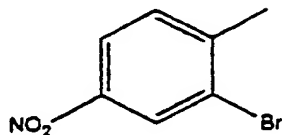
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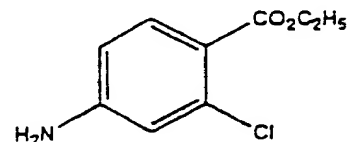
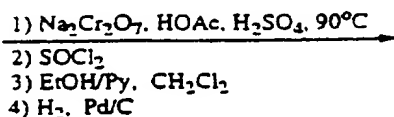
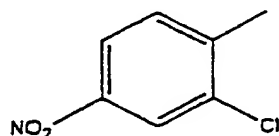
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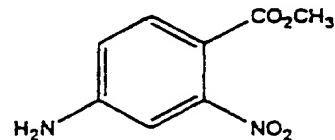
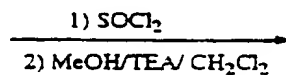
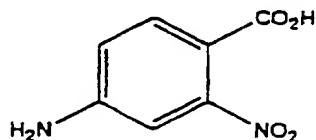
Compound C1



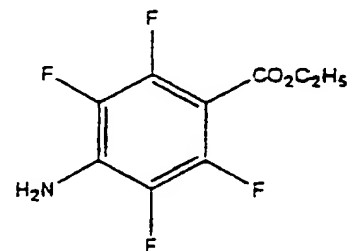
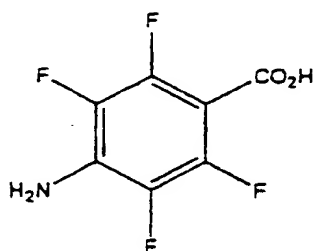
Compound D1



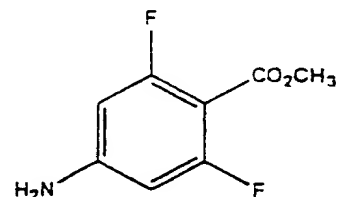
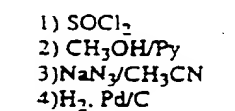
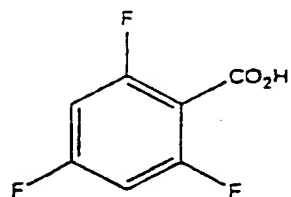
Compound E1



Compound F1



Compound G1



Compound H1

Reaction Scheme 6

1        Thus, in accordance with **Reaction Scheme 6**,  
2        3-nitro-6-methyl-fluorobenzene (Aldrich) is  
3        subjected to oxidation, conversion of the resulting  
4        carboxylic acid to an acid chloride and thereafter  
5        to an ethyl ester, followed by reduction of the  
6        nitro group, to yield ethyl  
7        2-fluoro-4-amino-benzoate (**Compound C<sub>1</sub>**).  
8        3-Nitro-6-methyl-bromobenzene (Aldrich) and  
9        3-nitro-6-methyl-chlorobenzene (Aldrich) are  
10       subjected to essentially to the same series of  
11       reactions to yield ethyl 2-bromo-4-amino-benzoate  
12       (**Compound D<sub>1</sub>**) and ethyl 2-chloro-4-amino-benzoate  
13       (**Compound E<sub>1</sub>**), respectively. 2-Nitro-4-aminobenzoic  
14       acid (Research Plus) is converted to its methyl  
15       ester (**Compound F<sub>1</sub>**) through the corresponding acid  
16       chloride. 2,3,5,6-Tetrafluoro-4-amino-benzoic acid  
17       (Aldrich) is esterified by treatment with ethanol in  
18       the presence of 1-(3-dimethylaminopropyl)-3-  
19       ethylcarbodiimide hydrochloride (EDC) and  
20       4-dimethylaminopyridine in CH<sub>2</sub>Cl<sub>2</sub> to give ethyl  
21       2,3,5,6-tetrafluoro-4-amino-benzoate (**Compound G<sub>1</sub>**).  
22       2,4,6-Trifluorobenzoic acid (Aldrich) is converted  
23       to the methyl ester through the acid chloride, and  
24       the 4-fluoro atom is displaced by reaction with  
25       sodium azide, followed by hydrogenation, to yield  
26       methyl 2,6-difluoro-4-amino benzoate (**Compound H<sub>1</sub>**).  
27       Compounds **C<sub>1</sub>**, **D<sub>1</sub>**, **E<sub>1</sub>**, **F<sub>1</sub>**, **G<sub>1</sub>** and **H<sub>1</sub>** serve as amine  
28       reagents in accordance with **Formula 7**. Further  
29       examples of reagents in accordance with **Formula 7**  
30       are nitro, fluoro, chloro, bromo and trifluoromethyl  
31       derivatives of amino substituted heteroaryl  
32       carboxylic acids, or their lower alkyl esters, such  
33       as ethyl 2-amino-4-chloropyridine 2-carboxylate,  
34       ethyl 5-amino-3-chloropyridine 5-carboxylate, and

1 3,4-dibromo-5-aminothiophene-2-carboxylic acid. The  
2 latter examples qcan be prepared by respective  
3 chlorination or bromination of  
4 2-aminopyridine-5-carboxylic acid or of its ester,  
5 3-aminopyridine-6-carboxylic acid or of its ester  
6 (described in WO 93/06086) and of  
7 2-aminothiophene-5-carboxylic acid (described in  
8 PCT/US92/06485).

9 The reactions between the compounds of **Formula 6**  
10 and **Formula 7** or between compounds of **Formula 6a** and  
11 **7a**, described above, comprise the actual syntheses  
12 of the carbamoyl (amide) compounds of the invention.  
13 Numerous examples of this reaction are described in  
14 detail in the experimental section below. The  
15 carbamoyl (amide) compounds of the invention can be  
16 converted into thiocarbamoyl (thioamide) compounds  
17 of the invention where with reference to **Formula 1 Z**  
18 is S, by reacting the carbamoyl (amide) compound  
19 with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-  
20 diphosphetane-2,4-disulfide (Lawesson's reagent).  
21 This reaction is illustrated in **Reaction Scheme 7**  
22 for two specific examples for the compounds used in  
23 the methods of the invention.

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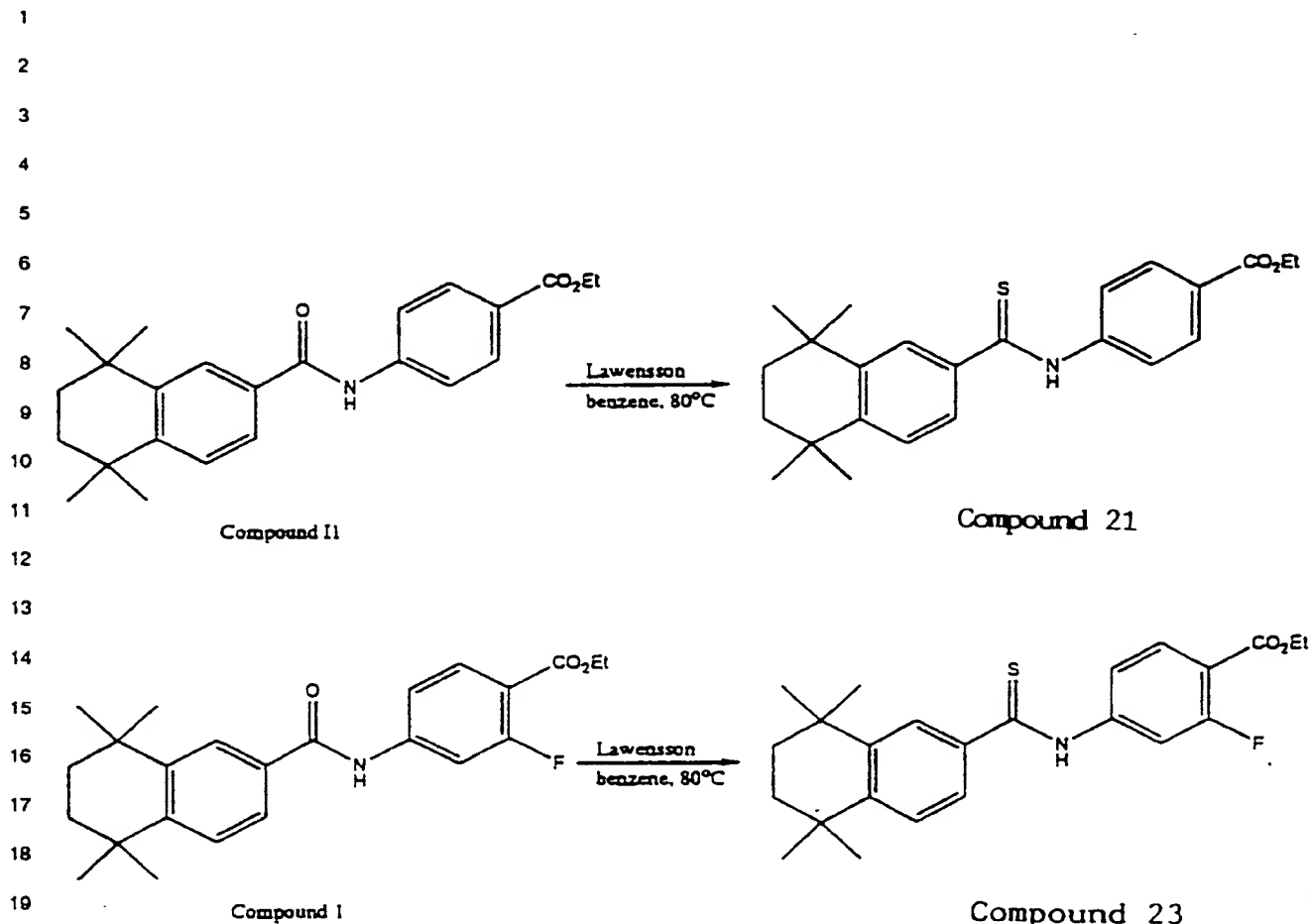
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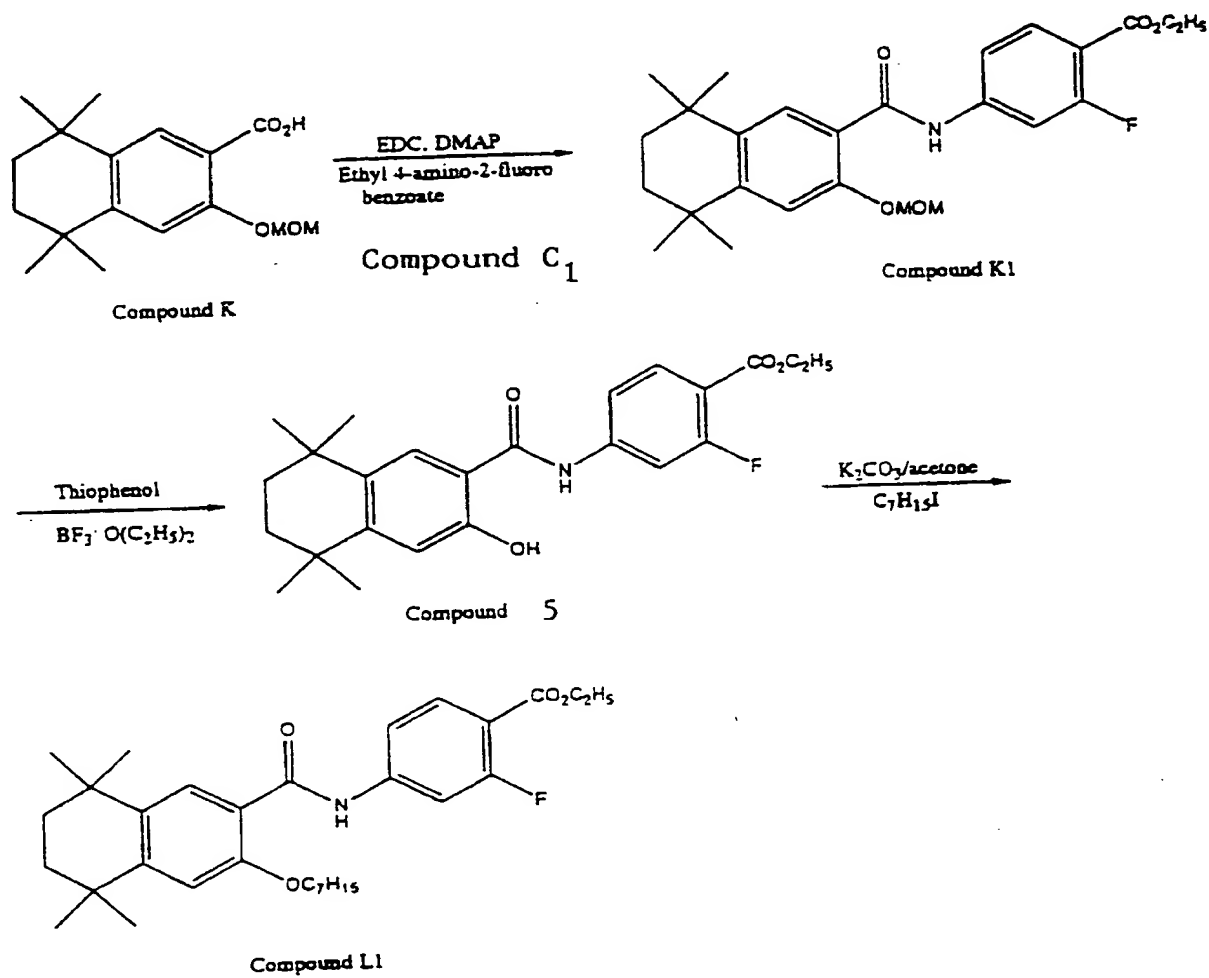
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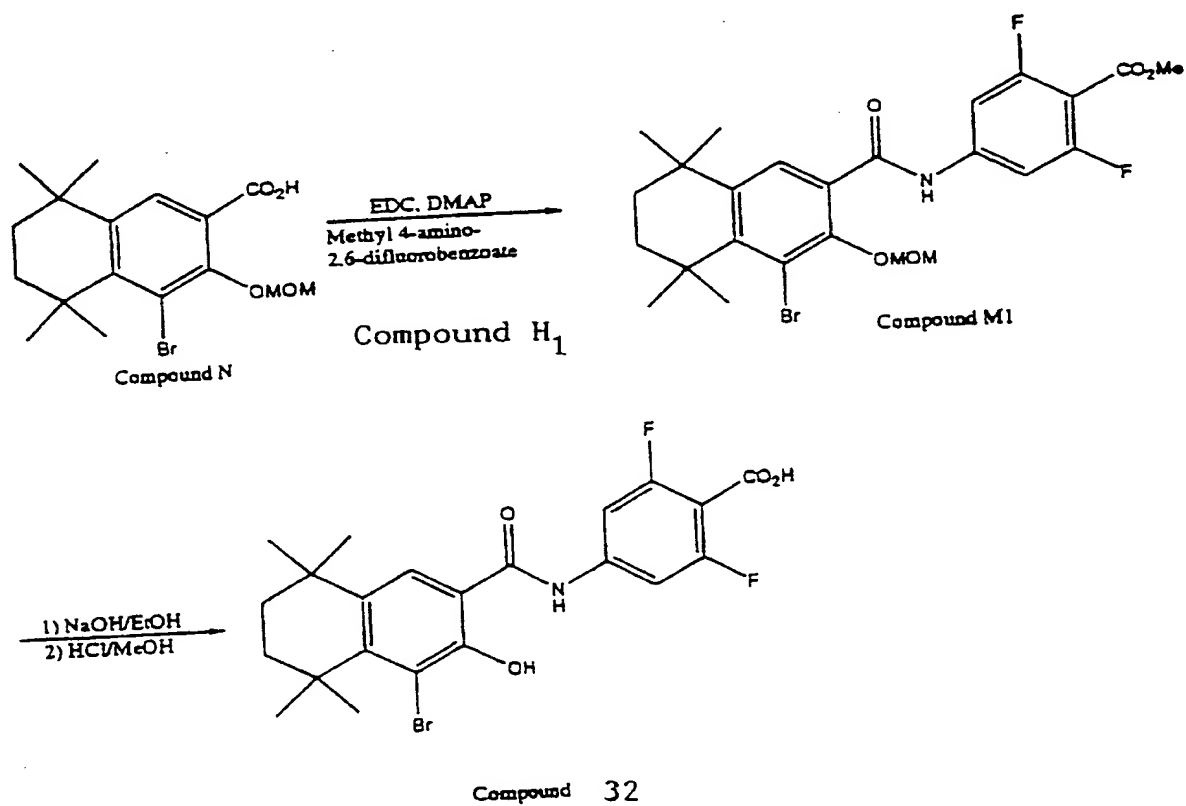
### Reaction Scheme 7

25 In Reaction Scheme 7 one starting material ethyl  
26 4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-  
27 naphthalen-2-yl]carbamoyl]benzoate (**Compound I<sub>1</sub>**) is  
28 obtained in accordance with the teachings of  
29 Kagechika et al. J. Med Chem. 1988 31, 2182 - 2192.  
30 The other starting material, ethyl  
31 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra  
32 methyl-naphthalen-2-yl]carbamoyl]benzoate (**Compound**  
33 **1**) is obtained in accordance with the present  
34 invention.

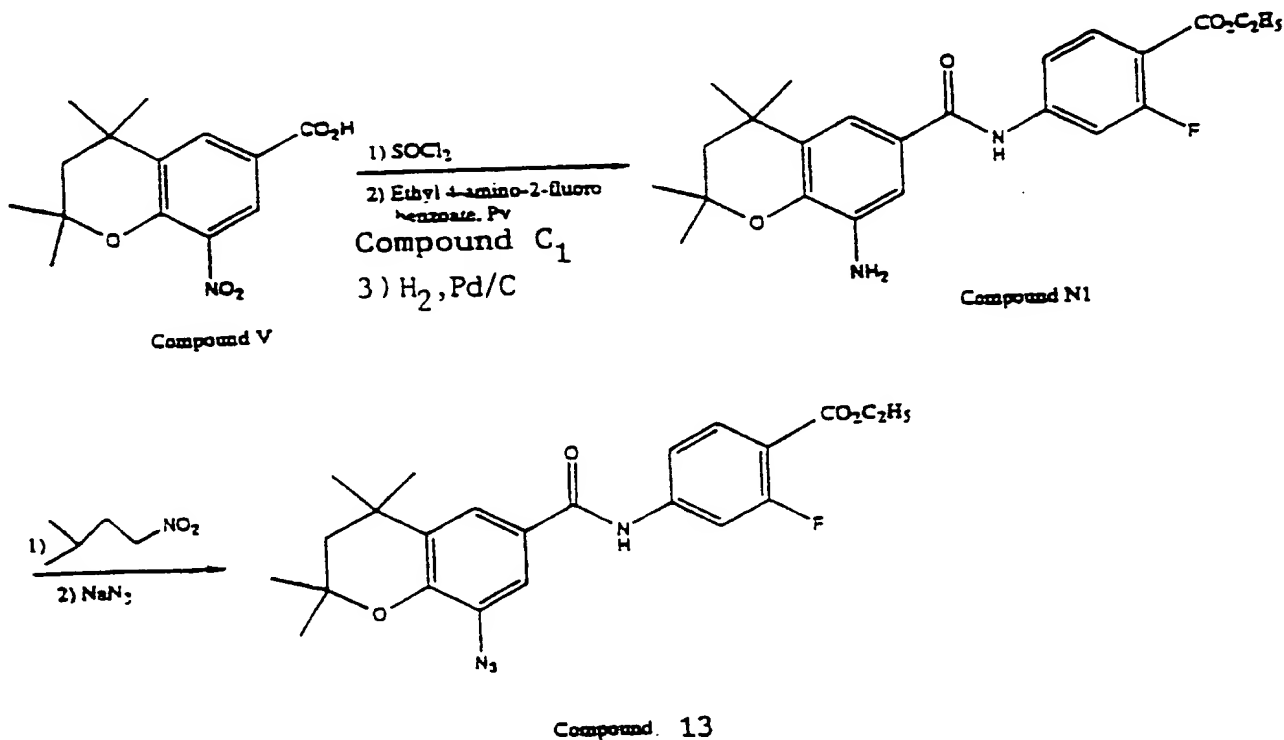


Reaction Scheme 8





Reaction Scheme 9



### Reaction Scheme 10

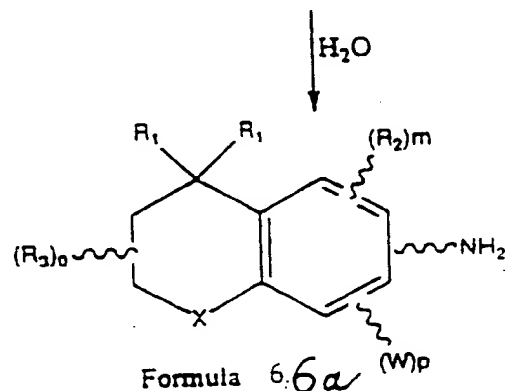
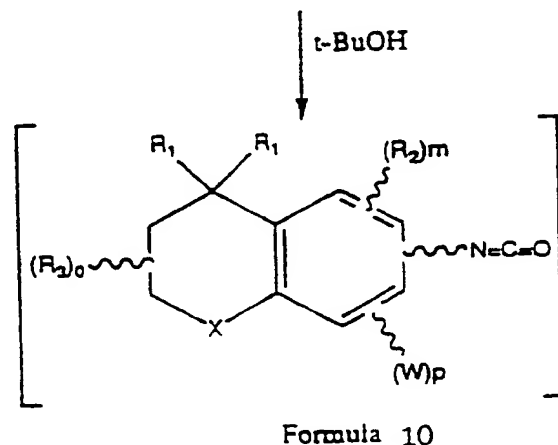
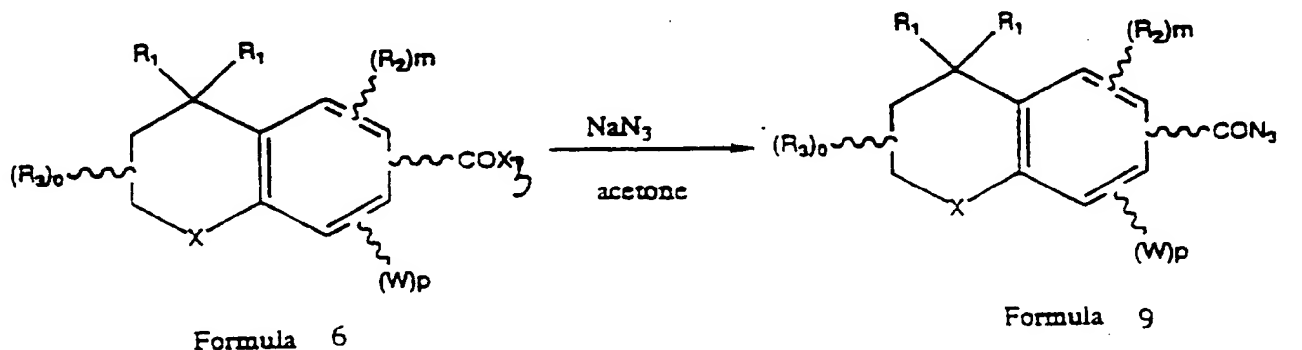
Reaction Schemes 8, 9 and 10 disclose examples for the preparation of carbamoyl (amide) compounds of the invention, first by a coupling reaction of a compound of Formula 6 with a compound of Formula 7, followed by one or more reactions performed on the carbamoyl (amide) compound that has been first obtained directly in the coupling reaction. Thus, as is shown in Reaction Scheme 8, 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymethoxynaphthalene-2-carboxylic acid (Compound K) is coupled with ethyl 4-amino-2-fluorobenzoate (Compound  $\text{C}_1$ ) in  $\text{CH}_2\text{Cl}_2$  in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and dimethylaminopyridine (DMAP) to give ethyl

1 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra  
2 methyl-2'-methoxymethoxy-naphthalen-  
3 3'-yl)carbamoyl]benzoate (**Compound K<sub>1</sub>**). The  
4 methoxymethyl protecting group is removed from  
5 **Compound K<sub>1</sub>** by treatment with thiophenol and  
6 borontrifluoride etherate resulting in ethyl  
7 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra  
8 methyl-2'-hydroxy-naphthalen-3'-yl)carbamoyl]-  
9 benzoate (**Compound 5**). The hydroxy function of  
10 **Compound 5** is converted into an *n*-hexyl ether by  
11 treatment with hexyl iodide in the presence of mild  
12 base.

13 In accordance with **Reaction Scheme 9**  
14 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-bromo-2-met  
15 hoxymethoxynaphthalene-3-carboxylic acid (**Compound**  
16 **N**) is coupled with methyl 4-amino-2,6-difluoro-  
17 benzoate (**Compound H<sub>1</sub>**) in CH<sub>2</sub>Cl<sub>2</sub> solvent in the  
18 presence of ethylcarbodiimide hydrochloride (EDC)  
19 and DMAP to provide methyl  
20 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-  
21 tetramethyl-1'-bromo-2'-methoxymethoxy-naphthalen-3'  
22 -yl)carbamoyl]benzoate (**Compound M<sub>1</sub>**), from which the  
23 esterifying methyl group and the methoxymethyl  
24 protecting group are removed by treatment with base  
25 and acid, respectively to yield  
26 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-  
27 tetramethyl-1'-bromo-2'-hydroxy-naphthalen-3'-yl)car  
28 bamoyl]benzoic acid (**Compound 32**).

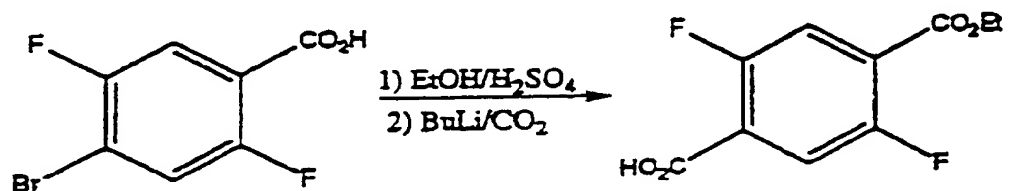
29 **Reaction Scheme 10** discloses the example of  
30 converting 2,2,4,4-tetramethyl-8-nitrochroman-6-  
31 carboxylic acid (**Compound V**) into the corresponding  
32 acid chloride by treatment with thionyl chloride,  
33 followed by coupling with ethyl  
34 4-amino-2-fluorobenzoate (**Compound C<sub>1</sub>**) and

hydrogenation to yield ethyl  
 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-6'-chr  
 omanyl)carbamoyl]benzoate (Compound N<sub>1</sub>). Compound N<sub>1</sub>  
 is converted to the corresponding 8-azido compound,  
 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-azido-  
 6'-chromanyl)carbamoyl]benzoate (Compound 13) by  
 treatment with isoamyl nitrate and NaN<sub>3</sub>.

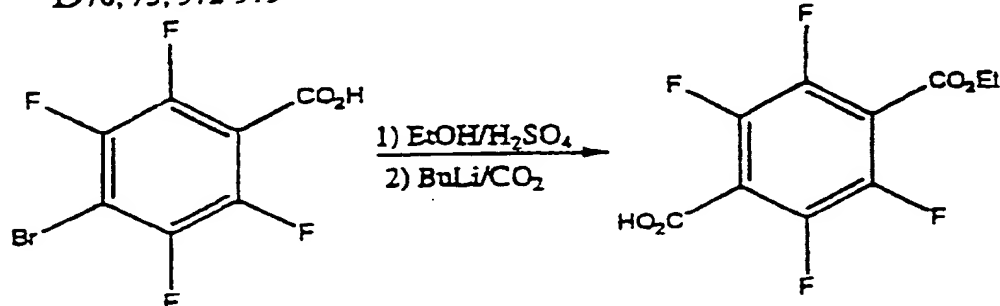


Reaction Scheme 11

Reaction Scheme 11 illustrates the synthesis of the primary amine compounds of Formula 6a from the acid chlorides ( $X_1 = Cl$ ) or other form of activated acids of Formula 6 where the primary amine of Formula 6a is not available by a published literature procedure. Thus, substantially in accordance with the step of a Curtius rearrangement, the acid chloride of Formula 6 is reacted with sodium azide in acetone to yield the azide compound of Formula 9. The azide of Formula 9 is heated in a polar high boiling solvent, such as t-butanol, to provide the intermediate isocyanate of Formula 10, which is hydrolyzed to yield a compound of Formula 6a.

Compound T<sub>1</sub>

Sugawara, S; Ishikawa, N.  
*Kogyo Kagaku Zasshi*  
1970, 73, 972-979

Compound V<sub>1</sub>

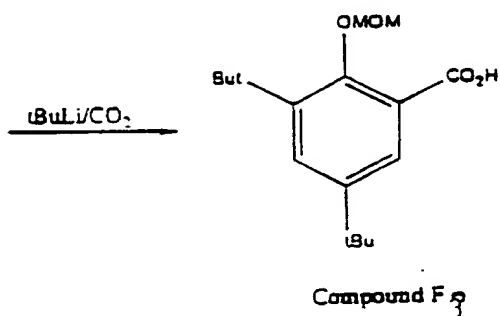
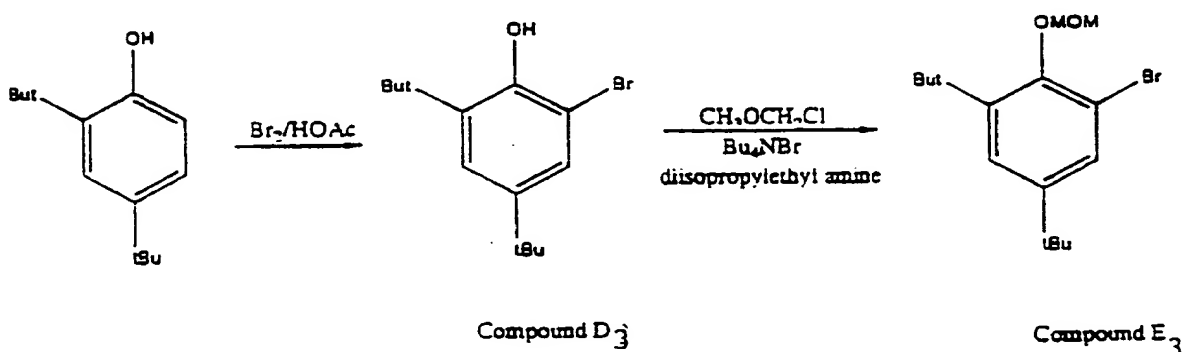
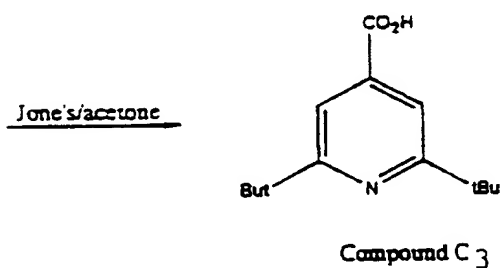
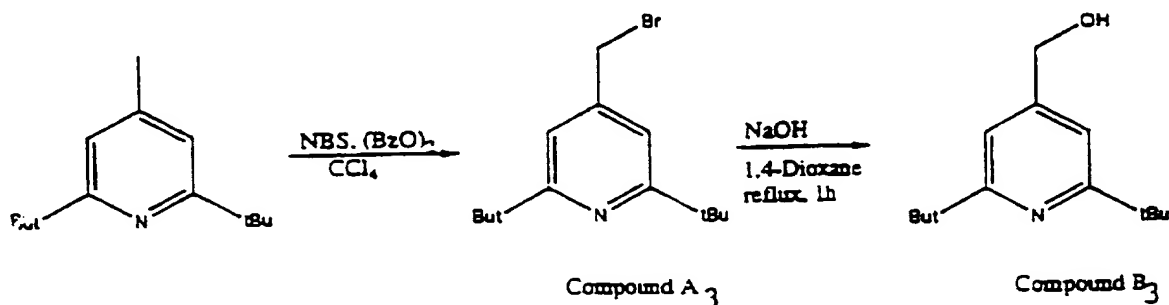
Michael Reuman et al  
*J. Med. Chem.*  
1995, 38, 2531-2540

Reaction Scheme 12

1       **Reaction Scheme 12** illustrates examples for  
2 preparing compounds of **Formula 7a** where such  
3 compounds are not available commercially or by a  
4 published literature procedure. Thus, by way of  
5 example 2,5-difluoro-4-bromobenzoic acid (available  
6 by the literature procedure of Sugawara et al. *Kogyo*  
7 *Kagaku Zasshi* 1970, 73, 972-979) is first esterified  
8 by treatment with ethyl alcohol and acid to yield  
9 the corresponding ester, and thereafter is reacted  
10 with butyl lithium followed by carbon dioxide to  
11 give the monoester of 2,5-difluoro terephthalic acid  
12 (**Compound T<sub>1</sub>**). A similar sequence of reactions  
13 performed on 2,3,5,6-difluoro-4-bromobenzoic acid  
14 (available by the literature procedure of Reuman et  
15 al. *J. Med. Chem.* 1995, 38, 2531-2540) yields the  
16 monoester of 2,3,5,6-tetrafluoroterephthalic acid  
17 (**Compound V<sub>1</sub>**). The just illustrated sequence of  
18 reaction can be, generally speaking, utilized for  
19 the synthesis of all compounds of **Formula 7a** with  
20 such modification which will become readily apparent  
21 to those skilled in the art, where such compounds  
22 are not available by a known literature procedure.

23       **Reaction Scheme 13** provides an example for the  
24 preparation of 2,6-di-tert-butylisonicotinic acid  
25 (**Compound C<sub>1</sub>**) which is a reagent in accordance with  
26 **Formula 8** for the preparation of several preferred  
27 compounds of the present invention. Thus,  
28 2,6-di-tert-butyl-4-methylpyridine (available  
29 commercially from Aldrich Chemical Co.) is reacted  
30 with N-bromosuccinimide and benzoyl peroxide to  
31 provide 4-bromomethyl-2,6-di-tert-butylpyridine  
32 (**Compound A<sub>1</sub>**). **Compound A<sub>1</sub>** is reacted with base  
33 (sodium hydroxyde) to yield the coresponding  
34 hydroxymethyl compound (**Compound B<sub>1</sub>**), which is

thereafter oxidized in a Jones oxidation reaction to give 2,6-di-tert-butylisonicotinic acid (Compound C<sub>3</sub>).

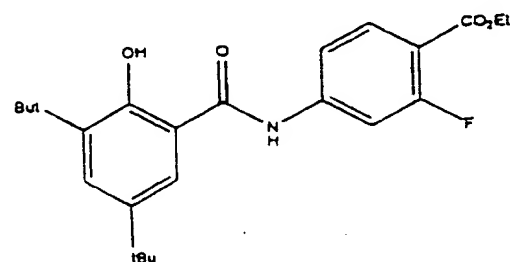
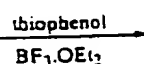
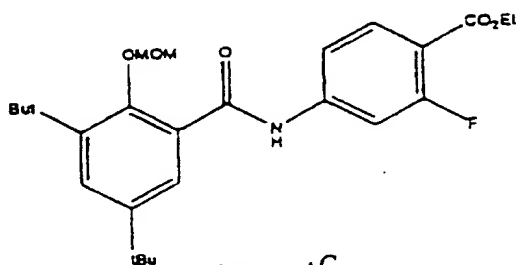
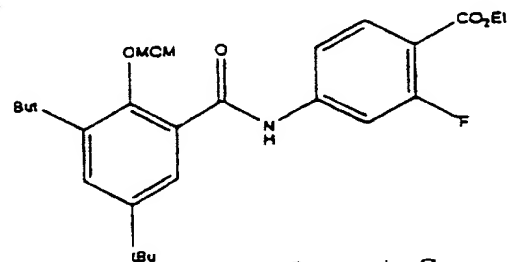
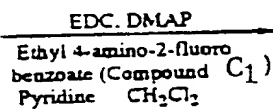
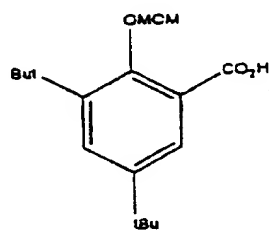
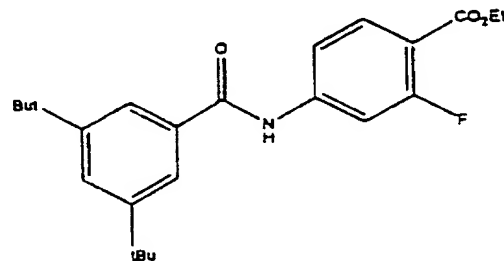
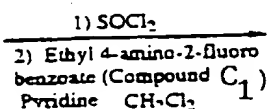
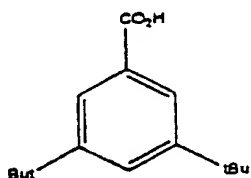
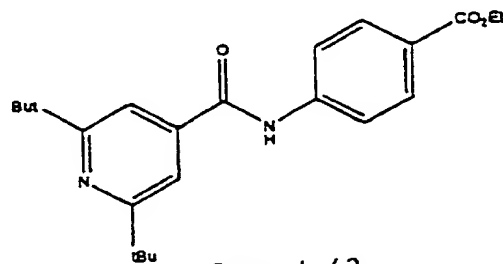
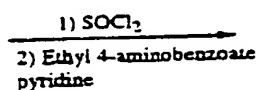
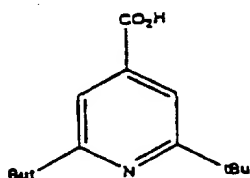
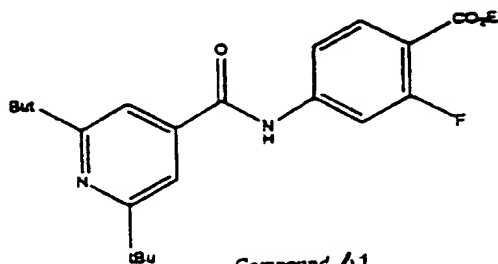
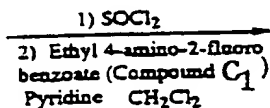
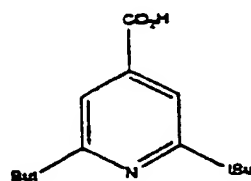


Reaction Scheme 13

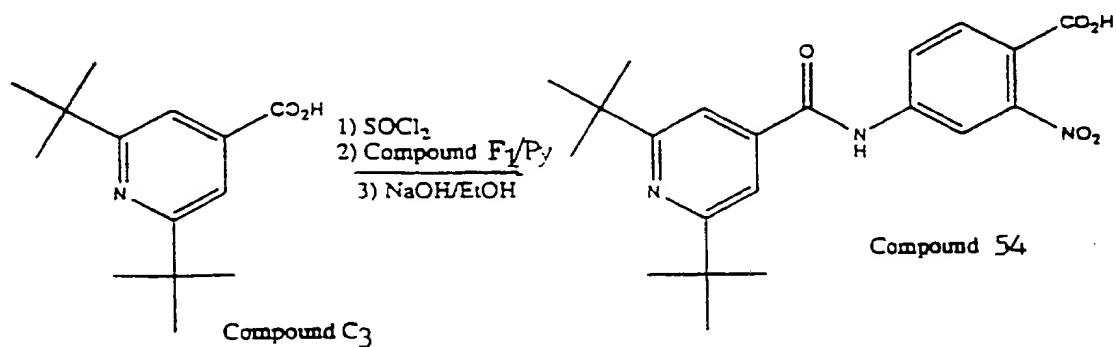
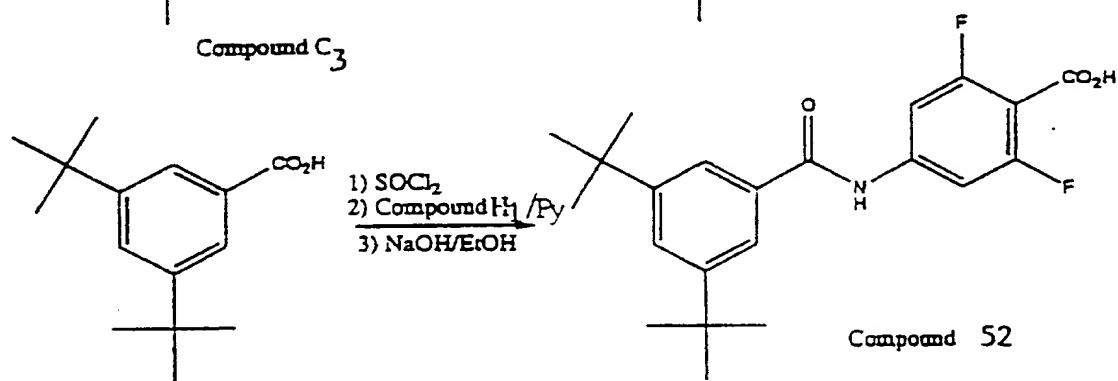
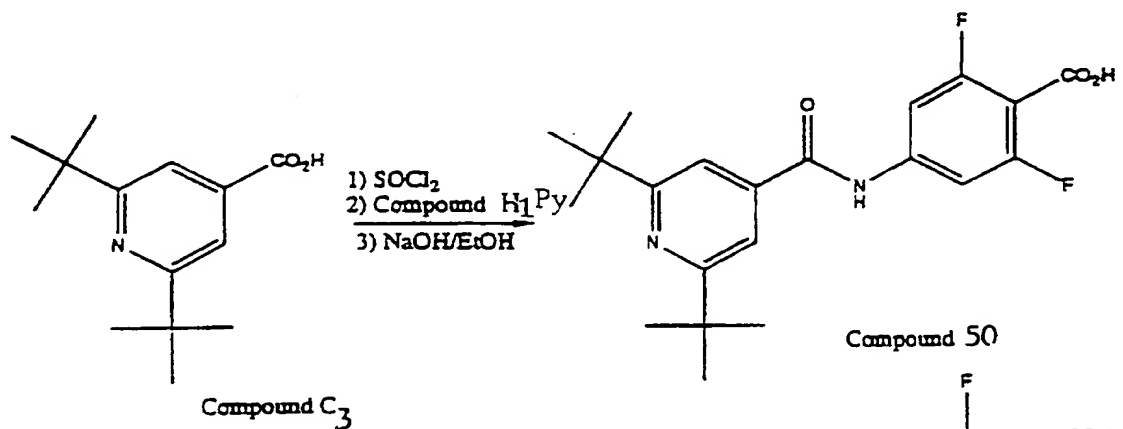
1       A further example of a compound which serves as  
2 a reagent for preparing the carbamoyl (or amide)  
3 compounds of the present invention is provided in  
4 **Reaction Scheme 13.** 2,4-Di-tert-butylphenol  
5 (Aldrich) is brominated in glacial acetic acid to  
6 yield 2-bromo-4,6-di-tert-butylphenol (**Compound D**),  
7 which is thereafter reacted with methoxymethyl  
8 chloride (MOMCl) to give  
9 O-methoxymethyl-2-bromo-4,6-di-tert-butylphenol  
10 (**Compound E**). **Compound E**, is treated with t-butyl  
11 lithium followed by carbon dioxide to yield  
12 O-methoxymethyl-3,5-di-tert-butylsalicylic acid  
13 (**Compound F**). **Compound F**, is a reagent which  
14 differs from the compounds generally encompassed by  
15 **Formula 8** only in that the hydroxyl function of this  
16 compound is protected by the methoxymethyl (MOM)  
17 group. However, the methoxymethyl protecting group  
18 is removed after formation of the carbamoyl (amide)  
19 linkage, as exemplified in **Reaction Scheme 14.**  
20 Reaction of an aromatic bromo compound (such as  
21 **Compound D**), with t-butyl lithium followed by carbon  
22 dioxide is a preferred method for preparing several  
23 aromatic carboxylic acids in accordance with **Formula**  
24 **8** and **Formula 7a**, described in the present  
25 application.

26       The primary amine compounds of **Formula 8a** which  
27 are not available commercially or by a published  
28 literature procedure can be made from the acid  
29 chlorides ( $X_1 = Cl$ ) or other form of activated acids  
30 of **Formula 8** substantially in accordance with the  
31 steps of a Curtius rearrangement, in analogy to the  
32 reaction steps described above in connection with  
33 **Reaction Scheme 11.**





Reaction Scheme 14



1        **Reaction Scheme 14** illustrates examples for the  
2 formation of the carbamoyl (amide) compounds in  
3 accordance with **Formula 2**, by reaction of a reagent  
4 of **Formula 8** with a reagent of **Formula 7**. Thus,  
5 2,6-di-tert-butylisonicotinic acid (**Compound C<sub>3</sub>**) is  
6 reacted with thionyl chloride ( $\text{SOCl}_2$ ) to provide the  
7 intermediate acid chloride, which is then reacted  
8 with ethyl 2-fluoro-4-amino-benzoate (**Compound C<sub>1</sub>**) in  
9 the presence of an acid acceptor (pyridine) to yield  
10 ethyl 2-fluoro-4-[(2',6'-di-tert-butylpyrid-4'-  
11 yl)carbamoyl]benzoate (**Compound 41**). As another  
12 example, 3,5-di-tert-butylbenzoic acid (available by  
13 the literature procedure of Kagechika et al., J.  
14 Med. Chem. 1988, 31, 2182, incorporated herein by  
15 reference) is reacted with thionyl chloride,  
16 followed by ethyl 2-fluoro-4-amino-benzoate  
17 (**Compound C<sub>1</sub>**) to yield ethyl 2-fluoro-4-[(3',5'-di-  
18 tert-butylphenyl)carbamoyl]benzoate (**Compound 45**).  
19 As still another example, *O*-methoxymethyl-3,5-di-  
20 tert-butylsalicylic acid (**Compound F<sub>3</sub>**) is reacted with  
21 ethyl 2-fluoro-4-amino-benzoate (**Compound C<sub>1</sub>**) in the  
22 presence of 4-dimethylaminopyridine (DMAP) catalyst  
23 and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
24 hydrochloride (EDC) to give ethyl 2-fluoro-4-[(2'-  
25 methoxymethyl-3',5'-di-tert-butylphenyl)car-  
26 bamoyl]benzoate (**Compound G<sub>3</sub>**). The methoxymethyl  
27 protecting group is removed from **Compound G<sub>3</sub>** by  
28 treatment with borontrifluoride etherate and  
29 thiophenol to yield ethyl 2-fluoro-4-[(2'-hydroxy-  
30 3',5'-di-tert-butylphenyl)carbamoyl]benzoate  
31 (**Compound 47**).

32        In yet another example shown in **Reaction Scheme**  
33 **14**, 2,6-di-tert-butylisonicotinic acid (**Compound C<sub>3</sub>**)  
34 is reacted with thionyl chloride ( $\text{SOCl}_2$ ), the

1 resulting intermediate acid chloride is reacted with  
2 methyl 2,6-difluoro-4-amino benzoate (**Compound H<sub>1</sub>**),  
3 followed by saponification of the ester group, to  
4 yield 2,6-difluoro-4-[(2',6'-di-tert-butylpyrid-  
5 4'-yl)carbamoyl]benzoic acid (**Compound 50**).  
6 3,5-Di-tert-butylbenzoic acid is subjected to the  
7 same sequence of reactions to provide  
8 2,6-difluoro-4-[(3',5'-di-tert-butylphenyl)car-  
9 bamoyl]benzoic acid (**Compound 52**).

10 As yet another example, shown in **Reaction Scheme**  
11 **14**, 2,6-di-tert-butylisonicotinic acid (**Compound C<sub>3</sub>**)  
12 is reacted with thionyl chloride (SOCl<sub>2</sub>), followed by  
13 methyl 2-nitro-4-aminobenzoate (**Compound F<sub>1</sub>**) and  
14 saponification of the ester function to give  
15 2-nitro-4-[(2',6'-di-tert-butylpyrid-4'-yl)carbamoyl  
16 ]benzoic acid (**Compound 54**).

17 Numerous other reactions suitable for preparing  
18 compounds of the invention, and for converting  
19 compounds of **Formula 1** and/or of **Formula 2** into  
20 still further compounds which can be used in the  
21 methods of treatment of the present invention, and  
22 also for preparing the reagents of **Formula 6**,  
23 **Formula 7**, **Formula 8**, **Formula 6a**, **Formula 7a** and  
24 **Formula 8a** will become readily apparent to those  
25 skilled in the art in light of the present  
26 disclosure. In this regard the following general  
27 synthetic methodology, applicable for conversion of  
28 the compounds of **Formula 1** and/or of **Formula 2** into  
29 further homologs and/or derivatives, and also for  
30 preparing the reagents of **Formula 6**, **Formula 7**, and  
31 **8**, (as well as **6a**, **7a** and **8a**) is noted.

32 Carboxylic acids are typically esterified by  
33 refluxing the acid in a solution of the appropriate  
34 alcohol in the presence of an acid catalyst such as

1 hydrogen chloride or thionyl chloride.  
2 Alternatively, the carboxylic acid can be condensed  
3 with the appropriate alcohol in the presence of  
4 dicyclohexylcarbodiimide and dimethylaminopyridine.  
5 The ester is recovered and purified by conventional  
6 means. Acetals and ketals are readily made by the  
7 method described in March, "Advanced Organic  
8 Chemistry," 2nd Edition, McGraw-Hill Book Company, p  
9 810). Alcohols, aldehydes and ketones all may be  
10 protected by forming respectively, ethers and  
11 esters, acetals or ketals by known methods such as  
12 those described in McOmie, Plenum Publishing Press,  
13 1973 and Protecting Groups, Ed. Greene, John Wiley &  
14 Sons, 1981.

15 The acids and salts derived from compounds of  
16 **Formula 1** and **Formula 2** are readily obtainable from  
17 the corresponding esters. Basic saponification with  
18 an alkali metal base will provide the acid. For  
19 example, an ester may be dissolved in a polar  
20 solvent such as an alkanol, preferably under an  
21 inert atmosphere at room temperature, with about a  
22 three molar excess of base, for example, potassium  
23 or lithium hydroxide. The solution is stirred for  
24 an extended period of time, between 15 and 20 hours,  
25 cooled, acidified and the hydrolysate recovered by  
26 conventional means.

27 The amide (in **Formula 1** or **2 B** is  $\text{CONR}_9\text{R}_{10}$ ) may  
28 be formed by any appropriate amidation means known  
29 in the art from the corresponding esters or  
30 carboxylic acids. One way to prepare such compounds  
31 is to convert an acid to an acid chloride and then  
32 treat that compound with ammonium hydroxide or an  
33 appropriate amine.

34 Alcohols are made by converting the

1 corresponding acids to the acid chloride with  
2 thionyl chloride or other means (J. March, "Advanced  
3 Organic Chemistry", 2nd Edition, McGraw-Hill Book  
4 Company), then reducing the acid chloride with  
5 sodium borohydride (March, Ibid, pg. 1124), which  
6 gives the corresponding alcohols. Alternatively,  
7 esters may be reduced with lithium aluminum hydride  
8 at reduced temperatures. Alkylating these alcohols  
9 with appropriate alkyl halides under Williamson  
10 reaction conditions (March, Ibid, pg. 357) gives the  
11 corresponding ethers. These alcohols can be  
12 converted to esters by reacting them with  
13 appropriate acids in the presence of acid catalysts  
14 or dicyclohexylcarbodiimide and  
15 dimethylaminopyridine.

16 Aldehydes can be prepared from the corresponding  
17 primary alcohols using mild oxidizing agents such as  
18 pyridinium dichromate in methylene chloride (Corey,  
19 E. J., Schmidt, G., Tet. Lett., 399, 1979), or  
20 dimethyl sulfoxide/oxalyl chloride in methylene  
21 chloride (Omura, K., Swern, D., Tetrahedron, 1978,  
22 34, 1651).

23 Ketones can be prepared from an appropriate  
24 aldehyde by treating the aldehyde with an alkyl  
25 Grignard reagent or similar reagent followed by  
26 oxidation.

27 Acetals or ketals can be prepared from the  
28 corresponding aldehyde or ketone by the method  
29 described in March, Ibid, p 810.

30

31

### Specific Examples

#### Ethyl 4-Amino-2-fluorobenzoate (Compound C<sub>1</sub>)

To a mixture of 2-fluoro-4-nitrotoluene (1.0 g, 6.4 mmol, Aldrich) and Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (2.74 g, 8.4 mmol) in 13.7 ml of HOAc was added slowly 6.83 ml of H<sub>2</sub>SO<sub>4</sub>. This mixture was slowly heated to 90 °C for 1 h to give a greenish heterogeneous solution. The mixture was cooled to room temperature and diluted with ethyl acetate. The PH of the solution was adjusted to 4 with NaOH (aq.). The mixture was extracted with more ethyl acetate. The organic layer was washed with NaHCO<sub>3</sub> (sat.), then brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solution was concentrated to dryness which then was dissolved in 6 ml of SOCl<sub>2</sub>, and heated at 80 °C for 1 h. The excess of SOCl<sub>2</sub> was removed under reduced pressure and the residue was dissolved in 5 ml of CH<sub>2</sub>Cl<sub>2</sub>, 2 ml of EtOH and 2 ml of pyridine. The mixture was stirred at room temperature for 2 h and concentrated to dryness. Ethyl 2-fluoro-4-nitrobenzoate was obtained as a white solid after column chromatography of the residue with ethyl acetate/hexane (1/9). This solid was then dissolved in 10 ml of ethyl acetate, and Pd/C (50 mg) was added. Hydrogenation with a hydrogen balloon converted ethyl 2-fluoro-4-nitrobenzoate into the title compound.

<sup>1</sup>H NMR δ 7.77 (t, J = 8.4 Hz, 1H), 6.41 (dd, J<sub>1</sub> = 8.6, J<sub>2</sub> = 2.2 Hz, 1H), 6.33 (dd, J<sub>1</sub> = 13.0, J<sub>2</sub> = 2.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.3 (b, 2H), 1.37 (t, J = 7.1 Hz, 3H).

#### Methyl 4-Amino-2,6-difluorobenzoate (Compound H<sub>1</sub>)

A solution of trifluorobenzoic acid (150 mg, 0.85 mmol, Aldrich) in 0.5 ml of SOCl<sub>2</sub> was heated

1 under reflux for 2h. The reaction mixture was  
2 cooled to room temperature, and excess of  $\text{SOCl}_2$  was  
3 removed under reduced pressure. The residue was  
4 dissolved in 1 ml of pyridine and 0.2 ml of  
5 methanol. After stirring at room temperature for 30  
6 min, solvent was removed and the residue was  
7 purified by column chromatography (ethyl  
8 acetate/hexane 1/10) to give methyl trifluoro-  
9 benzoate as a colorless oil. This oil was then  
10 dissolved in 1 ml of  $\text{CH}_3\text{CN}$ , then a solution of  $\text{NaN}_3$ ,  
11 (100 mg, 1.54 mmol) in 0.5 ml of water was added.  
12 The reaction mixture was refluxed for two days.  
13 Salt was filtered and the remaining solution was  
14 concentrated to an oil. This oil was then dissolved  
15 in 1 ml of methanol, followed by a catalytic amount  
16 of Pd/C (10%, w/w). The reaction mixture was  
17 hydrogenated under a hydrogen balloon for 12 h.  
18 Catalyst was removed and the solution was  
19 concentrated to an oil. After column chromatography  
20 (ethyl acetate/hexane 1/3), the title product was  
21 obtained as colorless crystals.

22  $^1\text{H}$  NMR  $\delta$  6.17 (d,  $J = 10.44$  Hz, 2H), 4.2 (b, 2H),  
23 3.87 (s, 3H).

24 8-Bromo-2,2,4,4-tetramethyl-6-chromanoic acid  
25 (Compound P)

26 To a solution of 2,2,4,4-tetramethyl-6-chro-  
27 manoic acid (200 mg, 0.85 mmol) in 0.5 ml of AcOH  
28 was added  $\text{Br}_2$  (0.07 ml, 1.28 mmol). The resulting  
29 dark-orange solution was stirred at room temperature  
30 for overnight. The excess bromine was removed under  
31 reduced pressure. Then the solution was poured into  
32 5 ml of water and extracted with ethyl acetate  
33 (3x3ml). The combined ethyl acetate layers were  
34 further washed with  $\text{NaHCO}_3$  (sat.), brine and dried



1 over  $\text{MgSO}_4$ . After concentration, the residue was  
2 purified by column chromatography (silica gel, ethyl  
3 acetate/hexane 1/3) to yield the desired product  
4 (170 mg, as white solids.

5  $^1\text{H}$  NMR  $\delta$  8.11 (d,  $J = 2.2$  Hz, 1H), 8.00 (d,  $J = 2.2$   
6 Hz, 1H), 1.90 (s, 2H), 1.43 (s, 6H), 1.39 (s, 6H).

7 8-Iodo-2,2,4,4-tetramethyl-6-chromanoic Acid  
8 (Compound X)

9 To a solution of 2,2,4,4-tetramethyl-6-chro-  
10 manoic acid (66 mg, 0.28 mmol) in 0.8 ml of AcOH was  
11 added ICl (0.07 ml, 1.4 mmol). The resulting  
12 colored solution was stirred at room temperature for  
13 overnight. Following the same procedure as for the  
14 synthesis of 8-bromo-2,2,4,4-tetramethyl-6-  
15 chromanoic acid (Compound P), the reaction gave the  
16 title compound (107 mg) as white solids.

17  $^1\text{H}$  NMR  $\delta$  8.35 (d,  $J = 2.2$  Hz, 1H), 8.03 (d,  $J = 2.2$   
18 Hz, 1H), 1.87 (s, 2H), 1.43 (s, 6H), 1.38 (s, 6H).

19 2,2,4,4-Tetramethyl-8-trifluoromethylchroman-6-oic  
20 acid (Compound S)

21 A solution of 8-bromo-2,2,4,4-tetramethyl-6-  
22 chromanoic acid (Compound R, 150 mg, 0.48 mmol) in 1  
23 ml of  $\text{SOCl}_2$  was refluxed for 2 h. After cooling to  
24 room temperature, the excess of  $\text{SOCl}_2$  was removed  
25 under reduced pressure and the residue was dissolved  
26 in 1 ml of pyridine and 0.2 ml of methanol. The  
27 mixture was stirred at room temperature for 30 min.  
28 Solvent was removed and the residue was passed  
29 through a column (silica gel, ethyl acetate/hexane  
30 1/10) to give the methyl 8-bromo-2,2,4,4-tetra-  
31 methylchromanoate (158 mg) as a colorless oil. To a  
32 solution of this methyl ester in 3 ml of  
33 N-methylpyrrolidone (NMP) was added  $\text{NaCO}_2\text{CF}_3$  (502 mg,  
34 3.7 mmol) and CuI (350 mg, 1.84 mmol). The

1 resulting mixture was heated to 175 °C (bath temp)  
2 for 2 h. The resulting mixture was cooled to room  
3 temperature and poured into ice-water. The product  
4 was extracted into ethyl acetate (3x3ml). The  
5 combined organic layers were dried and concentrated  
6 to dryness. The crude material was purified by  
7 column chromatography (ethyl acetate/chloroform  
8 1/10) to give the title compound as a colorless oil  
9 (120 mg). This was hydrolyzed under standard  
10 conditions to give the title compound.

11 <sup>1</sup>H NMR δ 8.21 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1  
12 Hz, 1H), 1.92 (s, 2H), 1.41 (s, 12H).

13 Ethyl 8-Nitro-2,2,4,4-tetramethyl-6-chromanoate  
14 (Compound W)

15 Ethyl 2,2,4,4-tetramethyl-6-chromanoate (150 mg,  
16 0.57 mmol) was slowly added to 0.3 ml of conc. H<sub>2</sub>SO<sub>4</sub>  
17 at 0 °C. To this mixture was added very slowly 0.03  
18 ml of HNO<sub>3</sub>. The reaction mixture was stirred at 0 °C  
19 for 30 min and poured into ice-water. The product  
20 was extracted into 5 ml of ethyl acetate, washed  
21 with NaHCO<sub>3</sub> (sat.), brine and dried over MgSO<sub>4</sub>.  
22 After concentration, the product was purified by  
23 column chromatography (ethyl acetate/hexane 1/10) to  
24 yield 74 mg of light-yellow oil.

25 <sup>1</sup>H NMR δ 8.24 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1  
26 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.95 (s, 2H),  
27 1.43 (s, 6H), 1.42 (s, 6H), 1.40 (t, J = 7.1 Hz,  
28 3H).

29 2-Oxo-4,4,8-trimethylchroman (Compound P<sub>1</sub>)

30 In a 500 ml of round bottom flask, NaH (1.66 g,  
31 60% suspension in oil, 0.046 mol) was washed with  
32 dry hexane. Then, dry THF (22 ml) was added  
33 followed by *o*-cresol (5 g, 0.046 mol) in 10 ml of  
34 dry THF. The reaction mixture was stirred at 0 °C

1 for 30 min followed by addition of 3,3-dimethyl  
2 acryloyl chloride in 10 ml of THF. The resulting  
3 white slurry was stirred at room temperature for 12  
4 h, then slowly quenched with water. The mixture was  
5 then extracted with ethyl acetate. The organic  
6 layer was washed with brine, water and dried over  
7  $\text{MgSO}_4$ . After filtration and removal of the solvent,  
8 a yellow oil was obtained (10.44 g). This oil was  
9 then dissolved in 50 ml of dry  $\text{CH}_2\text{Cl}_2$ , and was  
10 canulated into a solution of  $\text{AlCl}_3$  (10.8 g, 0.069  
11 mmol) in 10 ml of  $\text{CH}_2\text{Cl}_2$ . The reaction mixture was  
12 stirred at room temperature for 12 h. Then  
13 ice-water was carefully added and the organic layer  
14 was separated, and washed with  $\text{NaHCO}_3$  (sat), brine,  
15 water and finally dried over  $\text{MgSO}_4$ . After removal of  
16 the drying agent and solvent, the residue was  
17 purified by column chromatography (silica gel, ethyl  
18 acetate/hexane 1/9) to yield the title compound  
19 (4.408 g) as an oil.

20  $^1\text{H}$  NMR  $\delta$  7.1 (m, 3H), 2.62 (s, 2H), 2.33 (s, 3H),  
21 1.36 (s, 6H).

22 2,4-Dimethyl-4-(2'-hydroxy-3'-methylphenyl)pentan-2-  
23 ol (Compound  $\text{R}_1$ )

24 To a solution of 2-oxo-4,4,8-trimethylchroman  
25 (Compound  $\text{P}_1$ , 2.20 g, 11.5 mmol) in 40 ml of dry  
26 ethyl ether was added methyl magnesium bromide  
27 (12.67 ml, 38 mmol, 3 M solution in THF). The  
28 reaction mixture was stirred at room temperature for  
29 12 h, then quenched with  $\text{NH}_4\text{Cl}$  (sat.) until all  
30 precipitate dissolved. The mixture was extracted  
31 with diethyl ether and the combined organic layers  
32 were separated and washed with brine, water and  
33 dried over  $\text{MgSO}_4$ . After filtration and removal of  
34 the solvent, the title compound was obtained as a

1 tan solid (2.215 g).

2  $^1\text{H}$  NMR  $\delta$  7.16 (d,  $J = 7.88$  Hz, 1H), 7.00 (d,  $J = 6.72$   
3 Hz, 1H), 6.81 (t,  $J = 7.6$  Hz, 1H), 5.89 (b, 1H),  
4 2.21 (s, 3H), 2.17 (s, 2H), 1.48 (s, 6H), 1.10 (s,  
5 6H).

6 2, 2, 4, 4, 8-Pentamethyl-6-bromochroman (Compound  
7 Z) A solution of 2,4-dimethyl-4-(2'-hydroxy-3'-

8 methylphenyl)pentan-2-ol (Compound R<sub>1</sub>, 2.215 g, 9.98  
9 mmol) in 30 ml of 15% of  $\text{H}_2\text{SO}_4$  was heated to 110 °C.

10 After cooling to room temperature, the reaction  
11 mixture was extracted with diethyl ether. The  
12 organic layer was washed with  $\text{NaHCO}_3$  (sat.), brine  
13 and water. After filtration and removal of solvent,  
14 the residue was passed through a column (silica gel,  
15 pure hexane) to give the title compound as a clear  
16 oil (1.636 g). This oil was then dissolved in 1.5  
17 ml of HOAc, then  $\text{Br}_2$  (0.4113 ml, 7.98 mmol) was  
18 added. The reaction mixture was stirred at room  
19 temperature for 12 h. Solvent was removed under  
20 reduced pressure and to the residue was added ethyl  
21 acetate, and the resulting mixture was washed with  
22  $\text{NaHCO}_3$  (sat.), brine, water and dried over  $\text{MgSO}_4$ .  
23 After filtration and removal of solvent, the residue  
24 was passed through a column (silica gel, pure  
25 hexane) to give the title compound as a white solid  
26 (2.227 g).

27  $^1\text{H}$  NMR  $\delta$  7.21 (s, 1H), 7.06 (s, 1H), 2.14 (s, 3H),  
28 1.79 (s, 2H), 1.32 (s, 6H), 1.31 (s, 6H).

29 2,2,4,4,8-Pentamethyl-6-chromanoic Acid (Compound A<sub>1</sub>)

30 To a solution of 2,2,4,4, 8-pentamethyl-6-bromo-  
31 chroman (Compound Z) (1.2 g, 4.24 mmol) in 18 ml of  
32 dry THF at -78 °C under argon gas was added slowly  
33 5.48 ml of t-BuLi (1.7 M in hexane, 9.33 mmol). The  
34 reaction mixture was stirred at -78 °C for 1 h. Then

1 CO<sub>2</sub> was bubbled through the solution for 1 h. After  
2 removal of CO<sub>2</sub> stream, the reaction mixture was  
3 stirred for an additional hour at -78 °C. Then 10%  
4 of HCl was added. After warming up to room  
5 temperature, the reaction mixture was extracted with  
6 ethyl acetate. The organic layer was further washed  
7 with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After  
8 concentration, the residue was purified by column  
9 chromatography (ethyl acetate/hexane 5/95) to yield  
10 the title compound as a white solid (774 mg).

11 <sup>1</sup>H NMR δ 7.96 (s, 1H), 7.75 (s, 1H), 2.23 (s, 3H),  
12 1.88 (s, 2H), 1.39 (s, 6H).

13 8-Bromo-4,4-dimethyl-6-chromanoic Acid (Compound B<sub>1</sub>)

14 Using the same procedure as for the synthesis of  
15 8-bromo-2,2,4,4-tetramethylchromanoic acid (Compound  
16 P) but using 4,4-dimethylchromanoic acid (100 mg,  
17 0.49 mmol), the title compound was obtained as a  
18 white solid.

19 <sup>1</sup>H NMR δ 8.10 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.1  
20 Hz, 1H), 4.39 (t, J = 5.44 Hz, 2H), 1.89 (t, J = 5.4  
21 Hz, 1H), 1.38 (s, 6H).

22 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-5,5,8,8-  
23 tetramethylnaphthalene-3-carboxylate (Compound D)

24 To a solution of ethyl 5,6,7,8-tetrahydro-  
25 5,5,8,8-tetramethyl-3-aminonaphthalene-2-carboxylate  
26 (Compound C, 58 mg, 0.21 mmol) in 2 ml of HOAc was  
27 added Br<sub>2</sub> (0.02 ml, 0.42 mmol). The orange solution  
28 was stirred at room temperature for 2 days. The  
29 excess Br<sub>2</sub> and HOAc were removed under reduced  
30 pressure and the residue was passed through a column  
31 (silica gel, ethyl acetate/hexane 1/10) to yield the  
32 title compound as a light-orange oil (59 mg, 79.5%).

33 <sup>1</sup>H NMR δ 7.90 (s, 1H), 6.41 (b, 2H), 4.36 (q, J = 7.2  
34 Hz, 2H), 1.70 (m, 4H), 1.58 (s, 6H), 1.40 (t, J =

1 7.2 Hz, 3H), 1.28 (s, 6H).

2 Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl  
3 -4-bromonaphthalene-2-carboxylate (Compound E)

4 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-  
5 5,5,8,8-tetramethylnaphthalene-3-carboxylate  
6 (Compound D, 59 mg, 0.17 mmol) was dissolved in 2 ml  
7 of EtOH at 0°C. To this solution was added 1ml of  
8 trifluoroacetic acid and 1 ml of isoamylnitrite.  
9 The reaction mixture was stirred at 0°C for 30 min  
10 then H<sub>3</sub>PO<sub>2</sub> (0.325 ml, 3.14 mmol) was added. The  
11 reaction mixture was allowed to warm to room  
12 temperature and stirred for 12 h. NaHCO<sub>3</sub> (sat.) was  
13 added and the reaction mixture was extracted with  
14 ethyl acetate, dried over MgSO<sub>4</sub>, filtered and  
15 concentrated to give an oil. The product was  
16 purified by column chromatography (silica gel, ethyl  
17 acetate/hexane 1/10) to give the title compound as a  
18 colorless oil.

19 <sup>1</sup>H NMR δ 8.02 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0  
20 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.71 (m, 4H),  
21 1.56 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.31 (s,  
22 6H).

23 Ethyl  
24 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-fluoro-  
25 naphthalen-2-yl-carboxylate (Compound G)

26 In an ice bath, ethyl  
27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth  
28 alene-2-carboxylate (Compound C, 150 mg, 0.55 mmol)  
29 was added 0.24 ml of HBF<sub>4</sub> (48% solution in water),  
30 followed by a solution of NaNO<sub>2</sub> (81 mg, 1.16 mmol) in  
31 1 ml of water. The slurry was left in a  
32 refrigerator for 3 days. The reaction mixture was  
33 washed successively with ethyl acetate until TLC  
34 showed no UV visible spot at the baseline. The

1 ethyl acetate layer was dried with  $\text{MgSO}_4$  and the  
2 solution was concentrated to an oil. The oil was  
3 further dissolved in 1 ml of toluene and the mixture  
4 was heated under reflux for 2 h. After the reaction  
5 cooled to room temperature, solvent was evaporated  
6 and the residue was passed through a column (silica  
7 gel, ethyl acetate/hexane 1/10) to give the title  
8 compound as an oil.

9  $^1\text{H}$  NMR  $\delta$  7.85 (d,  $J = 7.8$  Hz, 1H), 7.04 (d,  $J = 12.3$   
10 Hz, 1H), 4.38 (q,  $J = 7.1$  Hz, 2H), 1.69 (s, 4H),  
11 1.38 (t,  $J = 7.1$  Hz, 3H), 1.30 (s, 6H), 1.28 (s,  
12 6H).

13 2-Bromo-3-hydroxy-5,5,8,8-tetrahydro-5,5,8,8-tetrame-  
14 thyl naphthalene (Compound I)

15 Using the same procedure as for the synthesis of  
16 8-bromo-2,2,4,4-tetramethyl-6-chromanoic acid  
17 (Compound P) but using 2-hydroxy-5,5,8,8-tetrahydro-  
18 5,5,8,8-tetramethyltetralin (700 mg, 3.43 mmol) and  
19  $\text{Br}_2$  (0.177 ml, 3.43 mmol) in 1.5 ml of HOAc, the  
20 title compound was obtained as a white solid (747  
21 mg).

22  $^1\text{H}$  NMR  $\delta$  7.36 (s, 1H), 6.96 (s, 2H), 5.32 (b, 1H),  
23 1.66 (s, 4H), 1.25 (s, 12H).

24 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-  
25 hoxy-2-bromonaphthalene (Compound J)

26 To a solution of 2-bromo-3-hydroxy-5,5,8,8-tet-  
27 rahydro-5,5,8,8-tetramethylnaphthalene (Compound I,  
28 600 mg, 2.12 mmol) and catalytic amount of  $\text{Bu}_4\text{NBr}$  in  
29 20 ml of dry  $\text{CH}_2\text{Cl}_2$  at 0 °C was added  
30 diisopropylethylamine (1.138 ml, 12.75 mmol),  
31 followed by methoxymethyl chloride (0.484 ml, 6.39  
32 mmol). The reaction mixture was heated at 45 °C for  
33 12 h. The reaction mixture was washed with 10% of  
34 citric acid, then  $\text{NaHCO}_3$  (sat.), brine and dried over

1 MgSO<sub>4</sub>. After filtration and removal of the solvent,  
2 the residue was purified by column chromatography  
3 (ethyl acetate/hexane 1/9) to yield the title  
4 compound (722 mg) as a white solid.

5 <sup>1</sup>H NMR δ 7.43 (s, 1H), 7.06 (s, 1H), 5.21 (s, 2H),  
6 3.54 (s, 3H), 1.66 (s, 4H), 1.26 (s, 6H), 1.25 (s,  
7 6H).

8 3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
9 naphthalen-2-yl carboxylic acid (Compound K)

10 Using the same procedure as for the synthesis of  
11 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound A<sub>1</sub>)  
12 but using 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
13 3-methoxymethoxy-2-bromonaphthalene (Compound J, 722  
14 mg, 2.21 mmol) and 2.86 ml of t-BuLi (4.87 mmol, 1.7  
15 M solution in hexane), the title compound was  
16 obtained as a white solid (143 mg).

17 <sup>1</sup>H NMR δ 8.12 (s, 1H), 7.19 (s, 1H), 5.40 (s, 2H),  
18 3.58 (s, 3H), 1.70 (s, 4H), 1.30 (s, 12H).

19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-  
20 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be-  
21 nzoate (Compound 1)

22 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
23 2-naphthoic acid (46 mg, 0.2 mmol) was added 1 ml  
24 thionyl chloride. This mixture was refluxed for 2  
25 h. Excess thionyl chloride was removed under  
26 reduced pressure and the residue was dissolved in 2  
27 ml of CH<sub>2</sub>Cl<sub>2</sub>. To this solution was added ethyl  
28 4-amino-2-fluorobenzoate ((Compound C<sub>1</sub>, 37 mg, 0.2  
29 mmol) followed by 0.5 ml of pyridine. The reaction  
30 mixture was stirred at room temperature for 4 h and  
31 was concentrated under reduced pressure. The  
32 residue was purified by column chromatography (ethyl  
33 acetate/hexane 1/10) to give the title compound as  
34 white solids.



<sup>1</sup>H NMR  $\delta$  8.06 (b, 1H), 7.93 (t,  $J$  = 8.4 Hz, 1H), 7.85 (d,  $J$  = 2.0 Hz, 1H), 7.78 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 12.9 Hz, 1H), 7.55 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 8.2 Hz, 1H), 7.40 (d,  $J$  = 8.3 Hz, 1H), 7.32 (dd,  $J_1$  = 2.02 Hz,  $J_2$  = 8.8 Hz, 1H), 4.38 (q,  $J$  = 7.2 Hz, 2H), 1.71 (s, 4H), 1.40 (t,  $J$  = 7.2 Hz), 1.32 (s, 6H), 1.30 (s, 6H).

Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-4'-bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound 3)

Using the same procedure as for the synthesis of ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound 1), but using 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphthalene-2-carboxylic acid (Compound F), the title compound was obtained as a white solid.

<sup>1</sup>H NMR  $\delta$  8.30 (b, 1H), 7.92 (t,  $J$  = 8.4 Hz, 1H), 7.84 (d,  $J$  = 2.1 Hz, 1H), 7.81 (d,  $J$  = 2.1 Hz, 1H), 7.74 (dd,  $J_1$  = 2.1 Hz,  $J_2$  = 12.8 Hz, 1H), 7.35 (dd,  $J_1$  = 2.0 Hz,  $J_2$  = 8.4 Hz, 1H), 4.36 (q,  $J$  = 7.2 Hz, 2H), 1.67 (m, 4H), 1.55 (s, 6H), 1.39 (t,  $J$  = 7.2 Hz, 3H), 1.31 (s, 6H).

Ethyl 2-Fluoro-4-[(3'-methoxymethoxy-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound R<sub>1</sub>)

Using the same procedure as for the synthesis of ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound S<sub>1</sub>), but using 3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl carboxylic acid

1 (Compound K, 143 mg, 0.49 mmol) and  
2 4-amino-2-fluorobenzoate (Compound C<sub>1</sub>, 98.5 mg, 0.54  
3 mmol), the title compound was obtained as a white  
4 solid.

5 <sup>1</sup>H NMR δ 10.1 (b, 1H), 8.20 (s, 1H), 7.93 (t, J = 8.8  
6 Hz, 1H), 7.83 (d, J = 13.4 Hz, 1H), 7.29 (d, J = 8.0  
7 Hz, 1H), 5.41 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H),  
8 3.59 (s, 3H), 1.70 (s, 4H), 1.31 (s, 12H), 1.26 (t,  
9 J = 7.1 Hz, 3H).

10 Ethyl 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-  
11 tetrahydro-5',5',8', 8'-tetramethyl-2-  
12 naphthalenyl)carbamoyl]benzoate (Compound 5)

13 A solution of ethyl 2-fluoro-4-[(3'-methoxymet-  
14 hoxy-5',6',7',8'-tetrahydro-5',  
15 5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]  
16 benzoate (Compound K<sub>1</sub>, 50.7 mg, 0.11 mmol) in 2 ml of  
17 CH<sub>2</sub>Cl<sub>2</sub> was added thiophenol (0.061 ml, 0.55 mmol).  
18 The reaction mixture was stirred at 0 °C for 5 min,  
19 then BF<sub>3</sub>.Et<sub>2</sub>O (0.027 ml, 0.22 mmol) was added. The  
20 reaction mixture was stirred at 0 °C for 2 h, then  
21 NaHCO<sub>3</sub> (sat.) was added. The organic layer was  
22 separated, and washed with brine, water and dried  
23 over MgSO<sub>4</sub>. After filtration and removal of solvent,  
24 the residue was passed through a column (silica gel,  
25 ethyl acetate/hexane 1/3) to give the title compound  
26 as white solid (44.2 mg).

27 <sup>1</sup>H NMR δ 8.61 (b, 1H), 7.94 (t, J = 8.42 Hz, 1H),  
28 7.71 (dd, J = 10.8, 2.0 Hz, 1H), 7.53 (s, 1H), 7.35  
29 (dd, J = 6.4, 2.0 Hz, 1H), 6.96 (s, 1H), 4.39 (q, J  
30 = 7.1 Hz, 2H), 1.69 (s, 4H), 1.40 (t, J = 7.1 Hz,  
31 3H), 1.29 (s, 6H), 1.27 (s, 6H).

32 Ethyl 2-Fluoro-4-[(4',4'-dimethyl-8'-bromochroman-  
33 6'-yl)carbamoyl]benzoate (Compound 7)

34 In a 10 ml of round bottom flask,

1 4,4-dimethyl-8-bromo-6-chromanoic acid (**Compound B<sub>1</sub>**,  
2 139 mg, 0.485 mmol) was added SOCl<sub>2</sub> (1 ml, large  
3 excess). The resulting solution was heated at 90 °C  
4 for 2 h and allowed to cool to room temperature.  
5 The excess of SOCl<sub>2</sub> was evaporated under reduced  
6 pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3  
7 ml). Ethyl 4-amino-2-fluorobenzoate (**Compound C<sub>1</sub>**, 90  
8 mg, 0.49 mmol) was added followed by pyridine (0.5  
9 ml, large excess). The reaction mixture was stirred  
10 for overnight and then concentrated to dryness. The  
11 residue was purified by column chromatography with  
12 ethyl acetate/hexane (1/5) to yield the title  
13 compound as a white solid (190 mg).

14 <sup>1</sup>H NMR δ 7.95 (t, J = 8.31 Hz, 1H), 7.88 (b, 1H),  
15 7.83 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H),  
16 7.75 (dd, J = 12.89, 2.0 Hz, 1H), 7.30 (dd, J =  
17 8.55, 2.0 Hz, 1H), 4.37 (m, 5H), 1.89 (t, J = 5.49  
18 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.39 (s, 6H).

19 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromo-  
20 chroman-6'-yl)carbamoyl]benzoate (Compound 9)

21 Using the same procedure as for ethyl  
22 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca  
23 rbamoyl]benzoate (**Compound 7**), but using  
24 2,2,4,4-tetramethyl-8-bromo-6-chromanoic acid  
25 (**Compound P**, 70 mg, 0.22 mmol) and ethyl  
26 4-amino-2-fluorobenzoate (**Compound C<sub>1</sub>**, 38 mg, 0.22  
27 mmol), the title compound was obtained as a white  
28 solid (80 mg, 76%).

29 <sup>1</sup>H NMR δ 8.25 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H),  
30 7.83 (s, 2H), 7.74 (dd, J<sub>1</sub> = 2.0, J<sub>2</sub> = 13.0 Hz, 1H),  
31 7.34 (dd, J<sub>1</sub> = 2.0, J<sub>2</sub> = 8.7 Hz, 1H), 4.37 (q, J =  
32 7.1 Hz, 2H), 1.88 (s, 2H), 1.41 (s, 6H), 1.39 (t, J  
33 = 7.1 Hz, 3H), 1.37 (s, 6H).

34 Ethyl

1 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoromet  
2 hylchroman-6'-yl)carbamoyl] benzoate (Compound 11)

3 Using the same procedure as for ethyl  
4 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca  
5 rbamoyl]benzoate (Compound 7), but using  
6 2,2,4,4-tetramethyl-8-trifluoromethyl-6-chromanoic  
7 acid (Compound S, 57 mg, 0.19 mmol) and ethyl  
8 4-amino-2-fluorobenzoate (Compound C<sub>1</sub>, 35 mg, 0.19  
9 mmol), the title compound was obtained as white  
10 solids.

11 <sup>1</sup>H NMR δ 8.06 (d, J = 2.2 Hz, 1H), 7.99 (b, 1H), 7.95  
12 (t, J = 8.55 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.76  
13 (dd, J = 12.8, 2.1 Hz, 1H), 7.33 (dd, J = 8.55, 1.9  
14 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.93 (s, 2H),  
15 1.41 (s, 12H), 1.40 (t, J = 7.2 Hz, 3H). Ethyl  
16 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-  
17 chroman-6'-yl)carbamoyl]benzoate (Compound N<sub>1</sub>)

18 Using 8-nitro-2, 2, 4,  
19 4-tetramethylchroman-6-carboxylic acid (Compound V)  
20 and following the same procedure as for the  
21 synthesis of ethyl 2-fluoro-4-[(4',4'-dimethyl-  
22 8'-bromochroman-6'-yl)carbamoyl]benzoate (Compound  
23 7), ethyl 2-fluoro-4-[2',2',4',4'-tetramethyl-  
24 8'-nitrochroman-6'-yl)]carbamoylbenzoate was  
25 obtained as a white solid. This compound (50 mg,  
26 0.12 mmol) was dissolved in 2 ml of methanol. A  
27 catalytic amount of Pd/C was added to the solution  
28 and the solution was maintained under H<sub>2</sub> atmosphere  
29 (hydrogen balloon) for overnight. The catalyst was  
30 removed by filtration and the solvent was evaporated  
31 to give the title compound as a white solid.

32 <sup>1</sup>H NMR δ 7.93 (t, J = 8.43 Hz, 1H), 7.90 (b, 1H),  
33 7.73 (dd, J = 12.9, 2.0 Hz, 1H), 7.29 (dd, J = 8.43,  
34 1.96 Hz, 1H), 7.23 (d, J = 2.14 Hz, 1H), 7.01 (d, J

1 = 2.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.88 (s,  
2 2H), 1.39 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.37  
3 (s, 6H).

4 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
5 azidochroman-6'-yl)carbamoyl]benzoate (Compound 13)

6 To a solution of ethyl  
7 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-aminochroman  
8 -6'-yl)carbamoyl]benzoate (Compound N<sub>1</sub>, 32 mg, 0.077  
9 mmol) in 3 ml of EtOH was added 0.5 ml of  
10 trifluoroacetic acid (TFA) and 0.5 ml of  
11 isoamylnitrite at 0°C. The reaction was stirred for  
12 2 h when a solution of NaN<sub>3</sub> (5 mg, ) in 0.2 ml of  
13 water was added. The reaction mixture was allowed  
14 to warm to room temperature and stirred for  
15 overnight. The solvent was removed and the residue  
16 was purified by column chromatography ( silica gel,  
17 ethyl acetate/ hexane 1/10) to give the title  
18 compound as a colorless oil.

19 <sup>1</sup>H NMR δ 8.0 (b, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.73  
20 (d, J = 12.1 Hz, 1H), 7.64 (s, 1H), 7.31 (dd, J =  
21 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 4.37 (q,  
22 J = 7.1 Hz, 2H), 1.90 (s, 2H), 1.39 (t, J = 7.1 Hz,  
23 3H), 1.45 (s, 6H), 1.40 (s, 6H).

24 Methyl  
25 2,6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluor  
26 omethylchroman-6'-yl)carbamoyl]benzoate (Compound  
27 15)

28 Using the same procedure as for ethyl  
29 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca  
30 rbamoyl]benzoate (Compound 7), but using  
31 2,2,4,4-tetramethyl-8-trifluoromethylchromanoic acid  
32 (Compound S, 11.2 mg, 0.037 mmol) and methyl  
33 4-amino-2,6-difluorobenzoate (Compound H<sub>1</sub>, 6.6 mg,  
34 0.035 mmol), the title compound was obtained as

1 white crystals.

2 <sup>1</sup>H NMR δ 8.21 (b, 1H), 8.05 (s, 1H), 7.82 (s, 1H),  
3 7.36 (d, J = 10.20 Hz, 1H), 3.93 (s, 3H), 1.92 (s,  
4 2H), 1.40 (s, 12H).

5 Ethyl 2-Fluoro-4-[(2', 2', 4',  
6 4'-tetramethyl-8'-iodochroman-6'-yl)carbamoyl]benzoa  
7 te (Compound 17)

8 Using the same procedure as for ethyl  
9 2-fluoro-4-[(4', 4'-dimethyl-8'-bromochroman-6'-yl)ca  
10 rbamoyl]benzoate (Compound 7), but using  
11 2,2,4,4-tetramethyl-8-iodochromanoic acid (Compound  
12 X, 81 mg, 0.25 mmol) and ethyl 4-amino-2-  
13 fluorobenzoate ((Compound C<sub>1</sub>, 55 mg, 0.30 mmol), the  
14 title compound was obtained as a white solid.

15 <sup>1</sup>H NMR δ 8.05 (b, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.94  
16 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.75  
17 (dd, J = 12.88, 2.1 Hz, 1H), 7.33 (dd, J = 8.8, 2.1  
18 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.89 (s, 2H),  
19 1.42 (s, 6H), 1.38 (s, 6H). Ethyl

20 2-Fluoro-4-[(2', 2', 4', 4', 8'-pentamethylchroman-  
21 6'-yl)carbamoyl]benzoate (Compound 19)

22 Using the same procedure as for ethyl  
23 2-fluoro-4-[(4', 4'-dimethyl-8'-bromochroman-6'-yl)ca  
24 rbamoyl]benzoate (Compound 9), but using  
25 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound  
26 A<sub>1</sub>, 92 mg, 0.37 mmol) and ethyl  
27 4-amino-2-fluorobenzoate (Compound C<sub>1</sub>, 75 mg, 0.41  
28 mmol), the title compound was obtained as a white  
29 solid (100 mg).

30 <sup>1</sup>H NMR δ 8.31 (b, 1H), 7.90 (t, J = 8.24 Hz, 1H),  
31 7.76 (dd, J = 14.29, 1.7 Hz, 1H), 7.74 (s, 1H), 7.43  
32 (s, 1H), 7.35 (dd, J = 8.67, 1.7 Hz, 1H), 4.32 (q, J  
33 = 7.1 Hz, 2H), 2.18 (s, 3H), 1.84 (s, 2H), 1.38 (t,  
34 J = 7.1 Hz, 3H), 1.35 (s, 6H), 1.34 (s, 6H).

1 Ethyl  
2 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-2  
3 -naphthalenyl)thiocarbamoyl]benzoate (Compound 21)

4 To a solution of ethyl  
5 4-[(5',6',7',8'-tetrahydro-5',5',8',  
6 8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate  
7 (Compound I<sub>1</sub>, 61 mg, 0.16 mmol) in 2 ml of anhydrous  
8 benzene was added Lawesson's reagent (45 mg, 0.112  
9 mmol). The resulting yellow solution was refluxed  
10 under N<sub>2</sub> for 2 h. The solvent was removed and the  
11 residue was purified by column chromatography  
12 (silica gel, ethyl acetate/hexane 1/5) to give the  
13 title compound as a yellow solid (55 mg, 87%).  
14 <sup>1</sup>H NMR δ 9.04 (b, 1H), 8.11 (d, J = 8.70 Hz, 2H),  
15 7.85 (b, 2H), 7.75 (b, 1H), 7.55 (dd, J = 8.2, 1.9  
16 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 4.38 (q, J = 7.1  
17 Hz, 2H), 1.71 (s, 4H), 1.40 (t, J = 7.1 Hz, 3H),  
18 1.30 (s, 12H).

19 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-  
20 5',5',8',8'-tetramethylnaphthalen-2'-yl)thiocarbamoy  
21 l]benzoate (Compound 23)

22 Using the same procedure as for the synthesis of  
23 ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-  
24 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate  
25 (Compound 21) but using ethyl  
26 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr  
27 amethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound  
28 1, 167 mg, 0.42 mmol) in 8 ml of benzene and  
29 Lawesson's reagent (220 mg, 0.544 mmol), the title  
30 compound was obtained as a bright yellow solid  
31 (127.5 mg).

32 <sup>1</sup>H NMR δ 9.30 (b, 1H), 8.05 (b, 1H), 7.95 (t, J =  
33 8.37 Hz, 1H), 7.77 (d, J = 1.89 Hz, 1H), 7.53 (dd, J  
34 = 8.24, 2.1 Hz, 1H), 7.49 (b, 1H), 7.35 (d, J = 8.24

1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 1H), 1.71. (s, 4H),  
2 1.32 (s, 6H), 1.30 (s, 6H).

3 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronap  
4 hthalen-2-yl carboxylic acid (Compound L)

5 To a solution of 2-bromo-3-methoxymethoxy-  
6 5,5,8,8-tetrahydro-5,5,8,8-tetramethylnaphthalene  
7 (Compound J, 722 mg, 2.2 mmol) in 10 ml of dry THF  
8 at -78°C under argon was added slowly 2.86 ml of  
9 t-BuLi (1.7 M in hexane, 4.8 mmol). The reaction  
10 mixture was stirred at -78°C for 1 h. Then CO<sub>2</sub> was  
11 bubbled through the solution for 1 h. After removal  
12 of CO<sub>2</sub> stream, the reaction mixture was stirred for  
13 an additional hour at -78°C. Then 10% of HCl was  
14 added. After warming up to room temperature, the  
15 reaction mixture was left overnight then extracted  
16 with ethyl acetate. The organic layer was washed  
17 with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After  
18 concentration, the residue was purified by column  
19 chromatography (ethyl acetate/hexane 1/3) to yield  
20 the title compound as a white solid.

21 <sup>1</sup>H NMR d 7.85 (s, 1H), 6.93 (s, 1H), 1.68 (s, 4H),  
22 1.28 (s, 12H).

23 4-Bromo-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetra  
24 ydronaphthalen-2-yl carboxylic acid (Compound M)

25 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
26 naphthalen-2-yl acid (Compound L, 155 mg, 0.62 mmol)  
27 was dissolved in 1 ml of HOAc. To this solution was  
28 added Br<sub>2</sub> (0.033 ml, 0.62 mmol). The reaction  
29 mixture was left at room temperature for over night.  
30 A stream of air was passed through the reaction  
31 mixture to remove the unreacted Br<sub>2</sub>. The remaining  
32 solid was dissolved in small amount of THF and  
33 purified by column chromatography (ethyl  
34 acetate/hexane 1/1) to yield the desired product as



1 a cream colored solid.

2 <sup>1</sup>H NMR d 7.91 (s, 1H), 1.75 (m, 2H), 1.64 (m, 2H),  
3 1.62 (s, 6H), 1.30 (s, 6H).

4 4-Bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8  
5 -tetrahydronaphthalen-2-yl carboxylic acid (Compound  
6 N)

7 To a solution of 4-bromo-3-hydroxy-5,5,8,8-  
8 tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl acid  
9 (Compound M), 233 mg, 0.71 mmol) in 6 ml of CH<sub>2</sub>Cl<sub>2</sub>,  
10 was added chloromethyl methyl ether (0.162 ml, 2.1  
11 mmol), diisopropylethyl amine (0.764 ml, 4.2 mmol)  
12 and a catalytic amount of tetrabutylammouimn  
13 bromide. The reaction mixture was heated to 45 °C  
14 for 2 h. The reaction mixture was concentrated and  
15 the residue was purified by column chromatography  
16 (ethyl acetate/hexane 1/9) to yield the  
17 methoxymethyl ester of the title compound as a white  
18 solid (200 mg). This white solid was further  
19 dissolved in 20 ml of EtOH. An aqueous solution of  
20 NaOH (0.5 ml, 1M) was added. The reaction mixture  
21 was stirred at room temperature for over night. The  
22 EtOH was removed and the residue was added 2 ml of  
23 ethyl acetate and 3 ml of water. This mixture was  
24 very slowly acidified with 10% HCl to PH = 7. The  
25 ethyl acetate layer was separated and washed with  
26 brine, dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration of the  
27 drying agent and removal of solvent, the reaction  
28 yielded the title compound as a white solid (155  
29 mg). <sup>1</sup>H NMR d 7.99 (s, 1H), 5.20 (s, 2H), 3.66 (s,  
30 3H), 1.74 (m, 2H), 1.67 (m, 2H), 1.60 (s, 6H), 1.32  
31 (s, 6H).

32 Ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-  
33 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth  
34 alen-2'-yl)carbamoyl]benzoate (Compound S<sub>1</sub>)

To a solution of 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl acid (**Compound N**, 80 mg, 0.22 mmol) in 4 ml of  $\text{CH}_2\text{Cl}_2$  was added DMAP (60 mg, 0.26 mmol), ethyl 2-fluoro-4-aminobenzoate (**Compound C<sub>1</sub>**, 43 mg, 0.24 mmol) and EDC (50 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for overnight and then concentrated to dryness. The residue was purified by column chromatography (ethyl acetate/hexane 1/3) to yield the title compound as a clear oil (45 mg).

$^1\text{H}$  NMR d 9.92 (b, 1H), 8.10 (s, 1H), 7.94 (t, J = 8.4 Hz, 1H), 7.81 (dd, J = 12.9; 1.9 Hz, 1H), 7.35 (dd, J = 8.5; 1.8 Hz, 1H), 5.20 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.61 (s, 3H), 1.74 (m, 2H), 1.64 (m, 2H), 1.60 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 1.34 (s, 6H).

#### Methyl

2,6-Difluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (**Compound M<sub>1</sub>**)

Using the same procedure as for the synthesis of compound ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate (**Compound S<sub>1</sub>**) but using 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl acid (**Compound N**, 80 mg, 0.22 mmol), DMAP (60 mg, 0.26 mmol), methyl 2,6-difluoro-4-aminobenzoate (**Compound H<sub>1</sub>**, 52 mg, 0.24 mmol) and EDC (50 mg, 0.26 mmol), the title compound was obtained as a clear oil.

$^1\text{H}$  NMR d 10.01 (b, 1H), 8.11 (s, 1H), 7.42 (d, J = 10.0 Hz, 2H), 5.2 (s, 2H), 3.95 (s, 3H), 3.63 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.35

1 (s, 6H).

2 4-Bromomethyl-2,6-di-*t*-butylpyridine (Compound A<sub>1</sub>)

3 To a mixture of 2,6-di-*t*-butyl-4-methylpyridine  
4 (Aldrich, 2.0 g, 9.73 mmol) in 25 ml of dry CCl<sub>4</sub> was  
5 added benzoyl peroxide (24 mg, 0.097 mmol) and NBS  
6 (1.9 g, 10.7 mmol). The reaction mixture was  
7 refluxed for 16 hours. After it cooled to room  
8 temperature, the solvent was removed in vacuo and  
9 the residue was purified by column chromatography  
10 (silica gel, hexane) to give an oil (1.957 g) which  
11 contained 82% of the desired product and 18% of the  
12 starting material. <sup>1</sup>H NMR δ 7.09 (s, 2H), 4.39 (s,  
13 2H), 1.35 (s, 18H).

14 4-Hydroxymethyl-2,6-di-*t*-butylpyridine (Compound B<sub>1</sub>)

15 A heterogeneous solution of  
16 4-bromomethyl-2,6-di-*t*-butylpyridine (Compound A<sub>1</sub>,  
17 1.743 g, 82% purity) in 20 ml of 12% NaOH in water  
18 and 10 ml of 1,4-dioxane was refluxed for 12 hours.  
19 The solution spontaneously separated into two layers  
20 as it cooled to room temperature. The upper layer  
21 was separated and ethyl acetate was added. This  
22 organic layer was then washed with brine, water and  
23 dried over MgSO<sub>4</sub>. The desired product was purified  
24 by column chromatography (ethyl acetate/hexane 1/9)  
25 to give a white solid. <sup>1</sup>H NMR δ 7.09 (s, 2H), 4.67  
26 (d, J = 4.4 Hz, 2H), 2.3 (b, 1H), 1.36 (s, 18H).

27 2,6-Di-*t*-butylisonicotinic acid (Compound C<sub>1</sub>)

28 Jone's reagent was added dropwise to a solution of  
29 4-hydroxymethyl-2,6-di-*t*-butylpyridine (Compound B<sub>1</sub>,  
30 302 mg, 1.37 mmol) in 5 ml of acetone until the  
31 solution changed color from light yellow to orange  
32 (55 drops of Jone's reagent were consumed). After 5  
33 minutes 2 ml of isopropanol were added to the  
34 reaction mixture, and a green precipitate of Cr<sup>3+</sup>

1 salt was formed. The precipitate was removed by  
2 filtration and the solution was diluted with ethyl  
3 acetate, then washed with brine, water and dried  
4 over  $\text{MgSO}_4$ . After filtration, the solvent was  
5 removed to give the desired product as a white solid  
6 (227 mg).  $^1\text{H}$  NMR  $\delta$  7.71 (s, 2H), 1.34 (s, 18H).

7 2-Bromo-4,6-di-*t*-butylphenol (Compound D<sub>1</sub>)

8 To a solution of 2,4-di-*t*-butylphenol (Aldrich,  
9 2.0 g, 9.7 mmol) in 2 ml of HOAc was added  $\text{Br}_2$  (0.5  
10 ml, 9.7 mmol). The reaction mixture was stirred at  
11 room temperature for 12 hours. Solvent was removed  
12 under reduced pressure and the residue was purified  
13 by column chromatography (ethyl acetate/hexane 1/20)  
14 to yield the desired product (2.54 g) as a white  
15 solid.  $^1\text{H}$  NMR  $\delta$  7.33 (d,  $J$  = 2.3 Hz, 1H), 7.24 (d,  $J$   
16 = 2.3 Hz, 1H), 1.41 (s, 9H), 1.29 (s, 9H).

17 O-Methoxymethyl-2-bromo-4,6-di-*t*-butylphenol  
18 (Compound E<sub>1</sub>)

19 To a solution of 2-bromo-4,6-di-*t*-butylphenol  
20 (Compound D<sub>1</sub>, 2.54 g, 8.88 mmol) and catalytic amount  
21 of  $\text{Bu}_4\text{NI}$  in 20 ml of dry  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added  
22 diisopropylethylamine (9.51 ml, 53 mmol), followed  
23 by methoxymethyl chloride (2.02 ml, 26.6 mmol). The  
24 reaction mixture was heated to  $45^\circ\text{C}$  for 12 hours.  
25 The reaction mixture was then washed with 10% citric  
26 acid, then  $\text{NaHCO}_3$  (sat.), brine, and dried over  
27  $\text{MgSO}_4$ . After filtration and removal of the solvent  
28 under reduced pressure, the residue was purified by  
29 column chromatography (pure hexane) to yield the  
30 title compound (2.79 g) as a colorless oil.  $^1\text{H}$  NMR  $\delta$   
31 7.40 (d,  $J$  = 2.44 Hz, 1H), 7.30 (d,  $J$  = 2.4 Hz, 1H),  
32 5.22 (s, 2H), 3.70 (s, 3H), 1.43 (s, 9H), 1.29 (s,  
33 9H).

34 O-Methoxymethyl-3',5'-di-*t*-butylsalicylic acid

1 (Compound F<sub>3</sub>)

2 To a solution of O-methoxymethyl-2-bromo-4,6-  
3 di-t-butylphenol (Compound E<sub>3</sub>, 2.79 g, 8.5 mmol) in  
4 30 ml of dry THF at -78°C under Ar was added 11 ml  
5 of t-BuLi (1.7 M in hexane, 18.7 mmol). This  
6 mixture was stirred at -78°C for 1 hour. Then CO<sub>2</sub>  
7 (g) was bubbled into the solution at -78°C for 1  
8 hour. After removal of the CO<sub>2</sub> stream, the reaction  
9 mixture was stirred for an additional hour at -78°C.  
10 Then 10% of HCl was added and the mixture was  
11 allowed to warm to room temperature and extracted  
12 with ethyl acetate. The organic layer was washed  
13 with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After  
14 concentration, the residue was purified by column  
15 chromatography (ethyl acetate/hexane 1/1) to yield  
16 the title compound as a white solid (492 mg). <sup>1</sup>H NMR  
17 δ 7.75 (d, J = 2.81 Hz, 1H), 7.60 (d, J = 2.8 Hz,  
18 1H), 5.07 (s, 2H), 3.62 (s, 3H), 1.33 (s, 9H), 1.26  
19 (s, 9H).

20 Ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-

21 yl)carbamoyl]benzoate (Compound 41)

22 A solution of 2,6-di-t-butylisonicotinic acid  
23 (Compound C<sub>3</sub>, 47.3 mg, 0.20 mmol) in 2 ml of SOCl<sub>2</sub>  
24 was heated under reflux for 2 hours. Excess SOCl<sub>2</sub>  
25 was removed in vacuo and the residue was dissolved  
26 in 2 ml of dry CH<sub>2</sub>Cl<sub>2</sub>, and ethyl  
27 2-fluoro-4-aminobenzoate (Compound C<sub>1</sub>, 40.2 mg, 0.22  
28 mmol) and pyridine (0.0835 ml, 0.69 mmol) were  
29 added. The reaction mixture was stirred at room  
30 temperature for 12 hours. Solvent was removed and  
31 the residue was purified by column chromatography  
32 (ethyl acetate/hexane 1/9) to yield the title  
33 compound (71.2 mg) as white crystals. <sup>1</sup>H NMR δ 8.56  
34 (b, 1H), 7.91 (t, J = 8.36 Hz, 1H), 7.53 (dd, J =

96

1 12.82, 2.0 Hz, 1H), 7.39 (dd, J = 8.7, 2.0 Hz, 1H),  
2 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H),  
3 1.35 (s, 18H).

4 Ethyl 4-[(2',6'-di-t-butylpyrid-4'-yl)car-  
5 bamoyl]benzoate (Compound 43)

6 Using the same procedure as for the synthesis of  
7 ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-  
8 yl)carbamoyl]benzoate (Compound 41) but using  
9 2,6-di-t-butylisonicotinic acid (Compound C<sub>3</sub>, 101 mg,  
10 0.43 mmol) and ethyl 4-aminobenzoate (78 mg, 0.47  
11 mmol), the title compound was obtained as a white  
12 solid (135 mg). <sup>1</sup>H NMR δ 8.43 (b, 1H),, 8.02 (d, J =  
13 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.48 (s, 2H),  
14 4.33 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H),  
15 1.35 (s, 18H).

16 Ethyl  
17 2-Fluoro-4-[(3',5'-di-t-butylphenyl)carbamoyl]benzoa  
18 te (Compound 45)

19 Using the same procedure as for the synthesis of  
20 ethyl 2-fluoro-4-[(2'6'-di-t-butylpyrid-4'-  
21 yl)carbamoyl]benzoate (Compound 41) but using  
22 3,5-di-t-butylbenzoic acid (60 mg, 0.26 mmol,  
23 available by literature procedure, see Kagechika et  
24 al. J. Med Chem. 1988 31, 2182 - 2192) and ethyl  
25 2-fluoro-4-aminobenzoate (Compound C<sub>1</sub>, 51.5 mg, 0.28  
26 mmol), the title compound was obtained as a white  
27 solid (66 mg). <sup>1</sup>H NMR δ 8.21 (b, 1H), 7.93 (t, J =  
28 8.3 Hz, 1H), 7.79 (dd, J = 12.8, 2.0 Hz, 1H), 7.67  
29 (d, J = 1.8 Hz, 2H), 7.65 (t, J = 1.7 Hz, 1H), 7.35  
30 (dd, J = 8.7, 2.1 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),  
31 1.39 (t, J = 7.2 Hz, 3H), 1.36 (s, 18H).

32 Ethyl  
33 2-Fluoro-4-[(2'-methoxymethyl-3',5'-di-t-butylphenyl  
34 )carbamoyl]benzoate (Compound G<sub>3</sub>)

1 To a mixture of O-methoxymethyl-3',5'-di-t-  
2 butylsalicylic acid (Compound F<sub>3</sub>, 150 mg, 0.51 mmol),  
3 4-dimethylaminopyridine (142 mg, 0.61 mmol) and  
4 ethyl 2-fluoro-4-aminobenzoate (Compound C<sub>1</sub>, 102 mg,  
5 0.56 mmol) in 5 ml of dry CH<sub>2</sub>Cl<sub>2</sub> was added 1-(3-di-  
6 methylaminopropyl)-3-ethylcarbodiimide hydrochloride  
7 (117 mg, 0.61 mmol). The reaction mixture was  
8 stirred at room temperature for 12 hours. Solvent  
9 was evaporated in vacuo and the residue was  
10 dissolved in ethyl acetate, then washed with brine,  
11 water and dried over MgSO<sub>4</sub>. After filtration,  
12 solvent was removed and the residue was purified by  
13 column chromatography (ethyl acetate/hexane 1/3) to  
14 give the title compound (58 mg). <sup>1</sup>H NMR δ 8.97 (b,  
15 1H), 7.94 (t, J = 8.37 Hz, 1H), 7.78 (d, J = 2.7 Hz,  
16 1H), 7.61 (d, J = 13.0 Hz, 1H), 7.56 (d, J = 2.6 Hz,  
17 1H), 7.35 (d, J = 8.7 Hz, 1H), 5.00 (s, 2H), 3.53  
18 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H),  
19 1.39 (t, J = 7.2 Hz, 3H), 1.33 (s, 9H).

20 Ethyl  
21 2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butylphenyl)carba  
22 moyl]benzoate (Compound 47)

23 To a solution of ethyl 2-fluoro-4-[(2'-  
24 methoxymethyl-3',5'-di-t-butylphenyl)carbamoyl]benzo  
25 ate (Compound G<sub>3</sub>, 34 mg, 0.07 mmol) in 1 ml of THF  
26 were added 10 drops of HOAc. The reaction mixture  
27 was heated to reflux for 12 hours. Solvent was  
28 removed and ethyl acetate was added. The solution  
29 was washed with NaCHO<sub>3</sub> (sat.), brine, water and dried  
30 over MgSO<sub>4</sub>. Solvent was removed in vacuo to give an  
31 oil. The oil was allowed to be exposed to the  
32 atmosphere for 12 hours during which time crystals  
33 formed. The crystals were collected and washed  
34 several times with hexane to afford the title

1 compound as a white solid (13.5 mg). <sup>1</sup>H NMR δ 10.73  
2 (s, 1H), 7.98 (d, J = 2.56 Hz, 1H), 7.88 (b, 1H),  
3 7.75 (t, J = 8.26 Hz, 1H), 7.60 (d, J = 2.44 Hz,  
4 1H), 7.32 (dd, J = 12.3, 2.0 Hz, 1H), 7.02 (dd, J =  
5 8.6, 2.0 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.39 (s,  
6 9H), 1.37 (t, J = 7.2 Hz, 3H), 1.5 (s, 9H).

7 2,6-Difluoro-4-[(2',6'-di-t-butylpyrid-4'yl)carbamoyl]  
8 benzoic Acid (Compound 50)

9 To 2,6-di-t-butylisonicotinic acid (Compound C<sub>3</sub>,  
10 20 mg, 0.085 mmol) was added 1 ml of SOCl<sub>2</sub>. The  
11 mixture was heated under reflux for 2 hours. After  
12 cooling to room temperature, excess SOCl<sub>2</sub> was removed  
13 and the residue was dissolved in 2 ml of CH<sub>2</sub>Cl<sub>2</sub>. To  
14 this solution was added methyl 2,6-difluoro-4-amino-  
15 benzoate (Compound H<sub>1</sub>, 16 mg, 0.085 mmol) and  
16 triethylamine (0.015 ml, 0.1 mmol). The reaction  
17 mixture was kept at room temperature for 2 hours and  
18 then concentrated to dryness. The residue was  
19 purified by column chromatography with ethyl  
20 acetate/hexane (1/10) to yield the methyl ester of  
21 the title compound. This was saponified according  
22 to the general procedure (see below) to give the  
23 title compound as a colorless solid. <sup>1</sup>H NMR δ 7.44  
24 (s, 2H), 7.40 (d, J = 11.8 Hz, 2H) 1.37 (s, 18H).

25 2,6-Difluoro-4-[(3',5'-di-t-butylphenyl)carbamoyl]  
26 benzoic Acid (Compound 52)

27 Using the same procedure as for the preparation  
28 of 2,6-difluoro-4-[(2',6'-di-t-butylpyrid-  
29 4'yl)carbamoyl]benzoic acid (Compound 50) but using  
30 3,5-di-t-butylbenzoic acid (37 mg, 0.16 mmol) and  
31 methyl 2,6-difluoro-4-aminobenzoate (Compound H<sub>1</sub>, 29  
32 mg, 0.16 mmol), the title compound was obtained as  
33 colorless crystals. <sup>1</sup>H NMR δ 7.92 (b, 1H) 7.60 (m,  
34 3H), 7.42 (d, J = 10.0 Hz, 2H), 1.38 (s, 18H).



1 2-Nitro-4-[(2',6'-di-*t*-butylpyrid-4'-yl)carbamoyl]be  
2 nzoic Acid (Compound 54)

3       Using the same procedure as for the preparation  
4 of 2,6-difluoro-4-[(2',6'-di-*t*-butylpyrid-  
5 4'-yl)carbamoyl]benzoic acid (Compound 50) but using  
6 2,6-di-*t*-butylisonicotinic acid (40 mg, 0.17 mmol)  
7 and methyl 2-nitro-4-aminobenzoate (Compound F<sub>1</sub>, 33  
8 mg, 0.17 mmol), the title compound was obtained as a  
9 light yellow oil. <sup>1</sup>H NMR δ (acetone-d<sub>6</sub>) 10.25 (b,  
10 1H), 8.32 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.93  
11 (b, 1H), 7.70 (s, 2H), 1.36 (s, 18H).

12 Methyl 2-nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-  
13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be  
14 nzoate (Compound 25)

15       Using the same procedure as for the synthesis of  
16 Compound 1, but using Compound F and Compound F<sub>1</sub>, the  
17 desired product was obtained as a white solid.  
18 <sup>1</sup>H NMR δ 9.24 (b, 1H), 9.23 (d, J = 1.8 Hz, 1H), 7.92  
19 (dd, J = 8.4, 2.4, Hz, 1H), 7.87 (d, J = 2.1 Hz,  
20 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.7 Hz,  
21 1H), 3.91 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.58  
22 (s, 3H), 1.33 (s, 3H).

23 General procedure for the syntheses of benzoic  
24 acid derivatives by hydrolyzing the corresponding  
25 methyl or ethyl esters.

26       To a solution of ester (3.0 mmol) in 20 ml of  
27 EtOH was added 5 ml of 1 N NaOH in water. The  
28 reaction mixture was stirred at room temperature for  
29 overnight and neutralized with 10% HCl to PH=5. The  
30 alcohol was removed by evaporation and the aqueous  
31 layer was extracted with ethyl acetate (3x10ml).  
32 The combined ethyl acetate layers were washed with  
33 NaHCO<sub>3</sub> (sat.), brine and dried over MgSO<sub>4</sub>. After  
34 concentration, the desired acid was obtained which

1 could be recrystallized in ethyl acetate or in  
2 acetonitrile.

3 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetra-  
4 amethylnaphthalen-2'-yl)carbamoyl]benzoic Acid  
5 (Compound 2)

6 <sup>1</sup>H NMR  $\delta$  (acetone-D<sub>6</sub>) 9.86 (b, 1H), 7.95 (m, 3H),  
7 7.75 (dd, J = 7.9, 2.2 Hz, 1H), 7.62 (dd, J = 8.5,  
8 1.6 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 1.73 (s, 4H),  
9 1.32 (s, 6H), 1.30 (s, 6H).

10 2-Fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8  
11 ',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic  
12 Acid (Compound 4)

13 <sup>1</sup>H NMR  $\delta$  (acetone-D<sub>6</sub>) 9.97 (b, 1H), 8.04 (d, J = 1.89  
14 Hz, 1H), 8.01 (d, J = 1.90 Hz, 1H), 7.95 (t, J =  
15 8.55 Hz, 1H), 7.90 (dd, J = 12.28, 2.0 Hz, 1H), 7.59  
16 (dd, J = 8.67, 1.50 Hz, 1H), 1.76 (m, 4H), 1.58 (s,  
17 6H), 1.35 (s, 6H).

18 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-tetrahydro-5',5'  
19 ,8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic  
20 Acid (Compound 6)

21 <sup>1</sup>H NMR (acetone-D<sub>6</sub>)  $\delta$  11.3 (b, 1H), 10.2 (b, 1H),  
22 7.94 (m, 2H), 7.85 (dd, J = 11.4, 1.95 Hz, 1H), 7.53  
23 (dd, J = 6.59, 2.08 Hz, 1H), 6.94 (s, 1H), 2.85 (b,  
24 1H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 12H).

25 2-Fluoro-4-[(8'-bromo-4',4'-dimethylchroman-6'-yl)ca  
26 rbamoyl]benzoic Acid (Compound 8)

27 <sup>1</sup>H NMR (acetone-d<sub>6</sub>)  $\delta$  9.87 (b, 1H), 8.04 (d, J = 2.1  
28 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.66  
29 Hz, 1H), 7.91 (dd, J = 13.8, 2.0 Hz, 1H), 7.57 (dd,  
30 J = 8.6, 2.0 Hz, 1H), 4.37 (t, J = 5.44 Hz, 2H),  
31 1.92 (t, J = 5.44 Hz, 2H), 1.40 (s, 6H).

32 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman  
33 -6'-yl)carbamoyl]benzoic Acid (Compound 10)

34 <sup>1</sup>H NMR  $\delta$  (acetone-d<sub>6</sub>) 9.87 (b, 1H), 8.06 (d, J = 2.2

1 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.54  
2 Hz, 1H), 7.91 (dd, J = 14.0, 2.0 Hz, 1H), 7.59 (dd,  
3 J = 8.5, 2.3 Hz, 1H), 1.96 (s, 2H), 1.42 (s, 6H),  
4 1.41 (s, 6H).

5 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoro-  
6 methylchroman-6'-yl)carbamoyl] benzoic Acid  
7 (Compound 12)

8 <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 10.02 (b, 1H), 8.31 (s, 1H),  
9 8.09 (s, 1H), 7.92 (m, 2H), 7.56 (d, J = 7.69 Hz,  
10 1H), 2.00 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

11 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-azidochroman  
12 -6'-yl)carbamoyl]benzoic Acid (Compound 14)

13 <sup>1</sup>H NMR δ 8.03 (t, J = 8.4 Hz, 1H), 7.87 (b, 1H), 7.79  
14 (dd, J = 13, 2.0 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H),  
15 7.32 (dd, J = 8.66, 1.9 Hz, 1H), 7.22 (d, J = 2.1  
16 Hz, 1H), 1.91 (s, 2H), 1.45 (s, 6H), 1.41 (s, 6H).

17 2, 6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-  
18 trifluoromethylchroman-6'-yl)carbamoyl]benzoic acid  
19 (Compound 16)

20 <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 8.30 (d, J = 2.3 Hz, 1H), 8.06  
21 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 10.32 Hz, 2H),  
22 1.954 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

23 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-iodochroman-  
24 6'-yl)carbamoyl]benzoic Acid (Compound 18)

25 <sup>1</sup>H NMR δ (acetone-d<sub>6</sub>) 10.0 (b, 1H), 8.24 (s, 1H),  
26 8.07 (s, 1H), 7.94 (m, 2H), 7.57 (d, J = 8.67 Hz,  
27 1H), 1.95 (s, 2H), 1.41 (s, 12H).

28 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-6'-yl  
29 )carbamoyl]benzoic Acid (Compound 20) <sup>1</sup>H NMR δ

30 (acetone-d<sub>6</sub>) 9.77 (b, 1H), 7.90 (m, 3H), 7.65 (d, J =  
31 2.0 Hz, 1H), 7.56 (dd, J = 8.61, 2.0 Hz, 1H), 2.19  
32 (s, 3H), 1.90 (s, 2H), 1.38 (s, 6H), 1.37 (s, 6H).

33 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna  
34 phthalen-2'-yl)thiocarbamoyl]benzoic Acid (Compound

1 22)

2 <sup>1</sup>H NMR δ 9.08 (b, 1H), 8.17 (d, J = 8.61, 2H), 7.95  
3 (b, 2H), 7.77 (b, 1H), 7.57 (dd, J = 8.1, 2.1 Hz,  
4 1H), 7.37 (d, J = 8.2 Hz, 1H), 1.72 (s, 4H), 1.32  
5 (s, 6H), 1.31 (s, 6H).

6 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr  
7 amethylnaphthalen-2'-yl)thiocarbamoyl]benzoic Acid  
8 (Compound 24)

9 <sup>1</sup>H NMR δ (acetone-d<sub>6</sub>) 11.1 (b, 1H), 8.27 (b, J = 13.2  
10 Hz, 1H), 8.02 (t, J = 8.3 Hz, 1H), 7.89 (s, 1H),  
11 7.86 (d, J = 10.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H),  
12 7.41 (d, J = 8.37 Hz, 1H), 1.72 (s, 4H), 1.30 (s,  
13 12H).

14 2-Fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahy  
15 dro-5',5',8',8'-tetramethylnaphthalen-2'-  
16 yl)carbamoyl]benzoic Acid (Compound 30)

17 A solution of ethyl 2-fluoro-4-[(3'-  
18 methoxymet-hoxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',  
19 ',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoa  
20 te (Compound S<sub>1</sub>, 45 mg, 0.084 mmol) in 1 ml of EtOH  
21 was added 1 ml of aqueous solution of NaOH (1M).  
22 The reaction mixture was stirred at room temperature  
23 for overnight and acidified to PH = 1 with 10% HCl.  
24 EtOH was removed and ethyl acetate and more water  
25 were added to the solution. The organic layer was  
26 separated and washed with NaHCO<sub>3</sub>, brine and dried  
27 over MgSO<sub>4</sub>. After filtration and concentration, the  
28 reaction yielded 2-fluoro-4-[(3'-methoxymethoxy-  
29 4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramet  
30 hyl naphthalen-2'-yl)carbamoyl]benzoic acid as a  
31 white solid. The methoxymethyl group was removed by  
32 dissolving the white solid in 2 ml of MeOH and 3  
33 drops of HCl (con.). After stirring for overnight,  
34 the reaction mixture was concentrated to dryness.

1 The residue was partitioned between ethyl acetate  
2 and water. The organic layer was separated, washed  
3 with  $\text{NaHCO}_3$ , brine and dried over  $\text{MgSO}_4$ . After  
4 filtration and concentration, the residual solid was  
5 purified in a mini (pipette) column with ethyl  
6 acetate /hexane (1/1) to give the title compound as  
7 a white solid (5.0 mg).

8  $^1\text{H}$  NMR d (acetone- $\text{d}_6$ ) 10.19 (b, 1H), 8.01 (s, 1H),  
9 7.96 (t,  $J = 8.6$  Hz, 1H), 7.76 (dd,  $J = 11.2$ ; 2.0  
10 Hz, 1H), 7.54 (dd,  $J = 8.8$ ; 2.0 Hz, 1H), 1.75 (m,  
11 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.32 (s, 6H).  
12 2,6-Difluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (Compound 32)

13  
14  
15 Using the same procedure as for the synthesis of  
16 2-fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic acid (Compound 30) the title compound was  
17  
18  
19 obtained as a white solid.

20  $^1\text{H}$  NMR d(acetone- $\text{d}_6$ ) 10.23 (b, 1H), 8.01 (s, 1H),  
21 7.52 (d,  $J = 10.2$  Hz, 2H), 4.8 (b, 1H), 1.75 (m,  
22 2H), 1.65 (m, 2H), 1.60 (s, 6H), 1.31 (s, 6H).

23 2,6-Difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid (Compound 34)

24  
25  
26 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
27 2-naphthoic acid (43 mg, 0.19 mmol) was added 1 ml  
28 of thionyl chloride. This mixture was refluxed for  
29 2 h. Excess thionyl chloride was removed under  
30 reduced pressure and the residue was dissolved in 2  
31 ml of  $\text{CH}_2\text{Cl}_2$ . To this solution was added methyl  
32 4-amino-2,6-difluorobenzoate (Compound H<sub>1</sub>, 7 mg, 0.2  
33 mmol) followed by 0.5 ml of pyridine. The reaction  
34 mixture was stirred at room temperature for 4 h and

1 was concentrated under reduced pressure. The  
2 residue was purified by column chromatography (ethyl  
3 acetate/hexane 1/5) to give the methyl ester of the  
4 desired product as a colorless oil.  
5  $^1\text{H}$  NMR  $\delta$  8.11 (d,  $J$  = 1.9 Hz, 1H), 8.05 (b, 1H), 7.86  
6 (dd,  $J$  = 6.2, 2.2 Hz, 1H), 7.41 (m, 3H), 3.93 (s,  
7 3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H). This  
8 colorless oil was hydrolyzed to the desired product  
9 with NaOH/H<sub>2</sub>O/EtOH according to the general  
10 procedure.

11  $^1\text{H}$  NMR  $\delta$  (acetone- $d_6$ ) 9.74 (b, 1H), 7.95 (s, 1H),  
12 7.70 (d,  $J$  = 6.8 Hz, 1H), 7.43 (d,  $J$  = 8.4 Hz, 3H),  
13 1.71 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).  
14 2-Nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8'  
15 ,8',-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic  
16 acid (Compound 26)

17  $^1\text{H}$  NMR  $\delta$  (acetone- $d_6$ ): 10.16 (b, 1H), 8.42 (d,  $J$  =  
18 2.0 Hz, 1H), 8.09 (dd,  $J$  = 8.6; 2.1 Hz, 1H), 8.06  
19 (d,  $J$  = 2.2 Hz, 1H), 8.04 (d,  $J$  = 2.2 Hz, 1H), 7.93  
20 (d,  $J$  = 8.6 Hz, 1H), 1.75 (m, 2H), 1.65 (m, 2H),  
21 1.57 (s, 3H), 1.34 (s, 3H).  
22 2-Fluoro-4-[(2',6'-di-*t*-butylpyrid-4'-yl)carbamoyl]b  
23 enzoic Acid (Compound 42)

24  $^1\text{H}$  NMR  $\delta$  (CD<sub>3</sub>OD) 7.92 (t,  $J$  = 8.36 Hz, 1H), 7.82  
25 (dd,  $J$  = 12.82, 2.0 Hz, 1H), 7.63 (s, 2H), 7.55 (dd,  
26  $J$  = 8.7, 2.1 Hz, 1H), 1.39 (s, 18H).

27 4-[(2',6'-Di-*t*-butylpyrid-4'-yl)carbamoyl]benzoic  
28 acid (Compound 44)

29  $^1\text{H}$  NMR  $\delta$  (CD<sub>3</sub>OD) 8.02 (d,  $J$  = 8.85 Hz, 2H), 7.85  
30 (d,  $J$  = 8.85 Hz, 2H), 7.63 (s, 2H), 1.40 (s, 18H).  
31 2-Fluoro-4-[(3',5'-di-*t*-butyl)phenylcarbamoyl]benzoi  
32 c acid (Compound 46)

33  $^1\text{H}$  NMR  $\delta$  (CD<sub>3</sub>OD) 7.92 (t,  $J$  = 8.3 Hz, 1H), 7.80  
34 (dd,  $J$  = 12.8, 2.0 Hz, 1H), 7.79 (d,  $J$  = 1.8 Hz,

1 2H), 7.69 (t, J = 1.7 Hz, 1H), 7.57 (dd, J = 8.7,  
2 2.1 Hz, 1H), 1.37 (s, 18H).

3 2-Fluoro-4-[(2'-hydroxy-3',5'-di-t-butyl)phenylcarba  
4 moyl]benzoic acid (Compound 48)

5 <sup>1</sup>H NMR  $\delta$  (acetone-d<sub>6</sub>) 12.3 (b, 1H), 10.07 (b,  
6 1H), 7.98 (t, J = 8.48 Hz, 1H), 7.80 (m, 2H), 7.58  
7 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.8, 2.0 Hz, 1H),  
8 1.44 (s, 9H), 1.31 (s, 9H).

**WHAT IS CLAIMED IS:**

1  
2       1. A process of administering to a mammal a  
3 retinoid compound which binds specifically or  
4 selectively to a  $RAR_{\alpha}$  retinoid receptors in  
5 preference over  $RAR_{\beta}$  and  $RAR_{\gamma}$  retinoid receptors, for  
6 the purpose of treating or preventing a disease or  
7 condition which is responsive to treatment by  $RAR_{\alpha}$   
8 specific or selective retinoid agonists.

9       2. A process in accordance with Claim 1 where  
10 the  $RAR_{\alpha}$  specific or selective retinoid compound  
11 binds approximately 500 times stronger to  $RAR_{\alpha}$   
12 retinoid receptors than to  $RAR_{\beta}$  and  $RAR_{\gamma}$  retinoid  
13 receptors.

14       3. A process in accordance with Claim 1 where  
15 the  $RAR_{\alpha}$  specific or selective retinoid compound is  
16 administered to a mammal for the treatment or  
17 prevention of the disease or condition selected from  
18 acute monocytic leukemia, cervical carcinoma,  
19 myeloma, ovarian carcinomas, head and neck  
20 carcinomas, proliferative vitreoretinopathy (PVR)  
21 and age related macular degeneration (AMD).

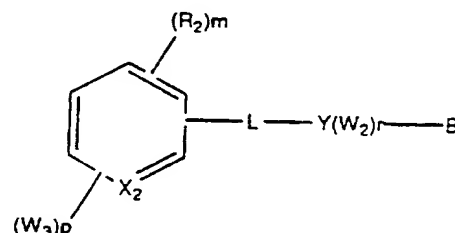
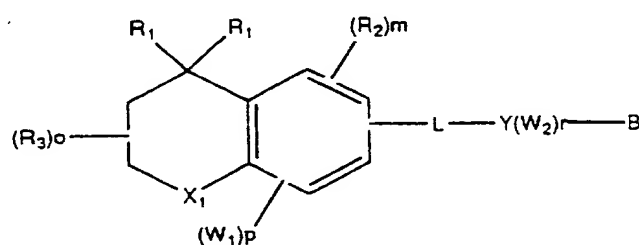
22       4. A process in accordance with Claim 3 where  
23 the  $RAR_{\alpha}$  specific or selective retinoid compound is  
24 administered in a dose of approximately 0.5 to 5 mg  
25 per kg body weight per day.

26       5. A process in accordance with Claim 1 where  
27 the  $RAR_{\alpha}$  specific or selective retinoid compound is  
28 administered to a mammal for the treatment or  
29 prevention of the disease or condition selected from  
30 actinic keratoses, arsenic keratoses, inflammatory  
31 and non-inflammatory acne, psoriasis, ichthyoses,  
32 eczema, atopic dermatitis, Darriers disease, lichen  
33 planus, glucocorticoid damage, topical microbial  
34 infection, skin pigmentation, age and photo damage



1 to the skin, premalignant and malignant  
 2 hyperproliferative diseases, Kaposi's sarcoma,  
 3 diseases of the eye, proliferative vitreoretinopathy  
 4 (PVR), retinal detachment, dry eye and other  
 5 corneopathies, cardiovascular diseases,  
 6 dyslipidemias, prevention of post-angioplasty  
 7 restenosis, diseases associated with human papilloma  
 8 virus (HPV), inflammatory diseases,  
 9 neurodegenerative diseases, improper pituitary  
 10 function, insufficient hair growth, diseases  
 11 associated with the immune system, and wound  
 12 healing.

13 6. A process in accordance with Claim 1 where  
 14 the  $RAR_n$  specific or selective retinoid compound has  
 15 the formula (i) or the formula (ii)  
 16  
 17  
 18  
 19



29 formula (i)

formula (ii)

30 where  $X_1$  is O or  $X_1$  is  $[C(R_1)_2]_n$  where n is an integer  
 31 between 0 and 2;

32  $R_1$  is independently H or alkyl of 1 to 6  
 33 carbons;

34  $R_2$  is independently hydrogen, or lower alkyl of

1 1 to 6 carbons;

2  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons or  
3 F;

4  $m$  is an integer having the value of 0 - 5;

5  $o$  is an integer having the value of 0 - 4;

6  $p$  is an integer having the value of 0 - 2;

7  $r$  is an integer having the value 0 - 2;

8  $X_2$  is N or CH;

9  $Y$  is a phenyl or naphthyl group, or heteroaryl  
10 selected from a group consisting of pyridyl,  
11 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
12 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said  
13 phenyl, naphthyl and heteroaryl groups being  
14 optionally substituted with one or two  $R_2$  groups;

15  $W_1$  is a substituent selected independently from  
16 the group consisting of F, Br, Cl, I, fluoro  
17 substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH, with the provisos  
18 that:

19 (i) when the compound is in accordance with  
20 **formula (i)** and  $Z$  is O then the sum of  $p$  and  $r$  is at  
21 least 1 and  $W_1$  is not a fluoro group in the 3  
22 position of a tetrahydronaphthalene ring;

23 (ii) when the compound is in accordance with  
24 **formula (i)** and  $r$  is zero and  $p$  is 1 and  $W_1$  is OH  
25 then the OH group is positioned  $\alpha$  to the L group;

26  $W_2$  is a substituent selected independently from  
27 the group consisting of F, Br, Cl, I, fluoro  
28 substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH;

29  $W_3$  is a substituent selected independently from  
30 the group consisting of F, Br, Cl, I,  $C_{1-6}$  alkyl,  
31 fluoro substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH with the  
32 proviso that when the compound is in accordance with  
33 **Formula 2** and  $X_2$  is CH and  $r$  is 0 then  $p$  is not 0 and  
34 at least one  $W_i$  group is not alkyl;

1 L is  $-(C=Z)-NH-$  or  $-NH-(C=Z)-$  Z is O or S,  
2 and

3 B is COOH or a pharmaceutically acceptable salt  
4 thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  
5  $CHO$ ,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ ,  
6 where  $R_7$  is an alkyl, cycloalkyl or alkenyl group  
7 containing 1 to 5 carbons,  $R_8$  is an alkyl group of 1  
8 to 10 carbons or trimethylsilylalkyl where the alkyl  
9 group has 1 to 10 carbons, or a cycloalkyl group of  
10 5 to 10 carbons, or  $R_8$  is phenyl or lower  
11 alkylphenyl,  $R_9$  and  $R_{10}$  independently are hydrogen,  
12 an alkyl group of 1 to 10 carbons, or a cycloalkyl  
13 group of 5-10 carbons, or phenyl or lower  
14 alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower  
15 alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is divalent  
16 alkyl radical of 2-5 carbons.

17 7. A process in accordance with Claim 6 where  
18 the  $RAR_a$  specific or selective retinoid compound is  
19 in accordance with formula (i).

20 8. A process in accordance with Claim 7 where  
21 in the formula of the  $RAR_a$  specific or selective  
22 retinoid compound  $X_1$  is  $[C(R_1)_2]_n$  and  $n$  is 1.

23 9. A process in accordance with Claim 8 where  
24 in the formula of the  $RAR_a$  specific or selective  
25 retinoid compound Y is phenyl.

26 10. A process in accordance with Claim 6 where  
27 the  $RAR_a$  specific or selective retinoid compound is  
28 in accordance with formula (ii).

29 11. A process in accordance with Claim 10 where  
30 in the formula of the  $RAR_a$  specific or selective  
31 retinoid compound Y is phenyl.

32 12. A process of administering to a mammal a  
33 retinoid compound which binds specifically or  
34 selectively to a  $RAR_a$  retinoid receptors in

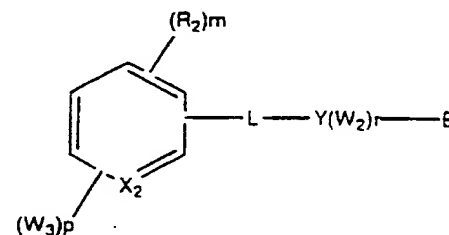
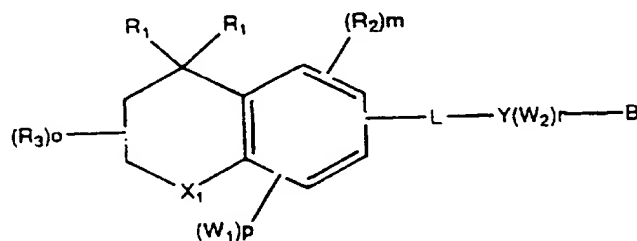
1 preference over  $RAR_{\beta}$  and  $RAR_{\gamma}$  retinoid receptors, for  
2 the purpose of treating or preventing a disease or  
3 condition which is responsive to treatment by  $RAR_{\alpha}$   
4 specific or selective retinoid agonists, the  
5 retinoid compound being specific or selective for  
6  $RAR_{\alpha}$  retinoid receptors in preference over  $RAR_{\beta}$  and  
7  $RAR_{\gamma}$  retinoid receptors when in a binding assay the  
8  $K_d$  value of binding to  $RAR_{\alpha}$  receptors is  
9 approximately 500 times smaller than the  $K_d$  value for  
10 binding to  $RAR_{\beta}$  and  $RAR_{\gamma}$  retinoid receptors.

11 13. A process in accordance with Claim 12 where  
12 the  $RAR_{\alpha}$  specific or selective retinoid compound is  
13 administered to a mammal for the treatment or  
14 prevention of the disease or condition selected from  
15 actinic keratoses, arsenic keratoses, inflammatory  
16 and non-inflammatory acne, psoriasis, ichthyoses,  
17 eczema, atopic dermatitis, Darriers disease, lichen  
18 planus, glucocorticoid damage, topical microbial  
19 infection, skin pigmentation, age and photo damage  
20 to the skin, premalignant and malignant  
21 hyperproliferative diseases, Kaposi's sarcoma,  
22 diseases of the eye, proliferative vitreoretinopathy  
23 (PVR), retinal detachment, dry eye and other  
24 corneopathies, cardiovascular diseases,  
25 dyslipidemias, prevention of post-angioplasty  
26 restenosis, diseases associated with human papilloma  
27 virus (HPV), inflammatory diseases,  
28 neurodegenerative diseases, improper pituitary  
29 function, insufficient hair growth, diseases  
30 associated with the immune system, and wound  
31 healing.

32 14. A process in accordance with Claim 13 where  
33 the  $RAR_{\alpha}$  specific or selective retinoid compound is  
34 administered to a mammal for the treatment or

prevention of the disease or condition selected from acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas, head and neck carcinomas, proliferative vitreoretinopathy (PVR) and age related macular degeneration (AMD).

15. A process in accordance with Claim 13 where the  $RAR_a$  specific or selective retinoid compound has the formula (i) or the formula (ii)



formula (i)

formula (ii)

where  $X_1$  is O or  $X_1$  is  $[C(R_1)_2]_n$  where  $n$  is an integer between 0 and 2;

$R_1$  is independently H or alkyl of 1 to 6 carbons;

$R_2$  is independently hydrogen, or lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 5;

$o$  is an integer having the value of 0 - 4;

$p$  is an integer having the value of 0 - 2;

$r$  is an integer having the value 0 - 2;

$X_2$  is N or CH;

1       Y is a phenyl or naphthyl group, or heteroaryl  
2 selected from a group consisting of pyridyl,  
3 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,  
4 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said  
5 phenyl, naphthyl and heteroaryl groups being  
6 optionally substituted with one or two R<sub>2</sub> groups;

7       W<sub>1</sub> is a substituent selected independently from  
8 the group consisting of F, Br, Cl, I, fluoro  
9 substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH, with the provisos  
10 that:

11       (i) when the compound is in accordance with  
12 **formula (i)** and Z is O then the sum of p and r is at  
13 least 1 and W<sub>1</sub> is not a fluoro group in the 3  
14 position of a tetrahydronaphthalene ring;

15       (ii) when the compound is in accordance with  
16 **formula (i)** and r is zero and p is 1 and W<sub>1</sub> is OH  
17 then the OH group is positioned α to the L group;

18       W<sub>2</sub> is a substituent selected independently from  
19 the group consisting of F, Br, Cl, I, fluoro  
20 substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH;

21       W<sub>3</sub> is a substituent selected independently from  
22 the group consisting of F, Br, Cl, I, C<sub>1-6</sub>alkyl,  
23 fluoro substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH with the  
24 proviso that when the compound is in accordance with  
25 **Formula 2** and X<sub>2</sub> is CH and r is 0 then p is not 0 and  
26 at least one W<sub>3</sub> group is not alkyl;

27       L is -(C=Z)-NH- or -NH-(C=Z)-

28       Z is O or S, and

29       B is COOH or a pharmaceutically acceptable salt  
30 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>,  
31 CHO, CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O,  
32 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group  
33 containing 1 to 5 carbons, R<sub>8</sub> is an alkyl group of 1  
34 to 10 carbons or trimethylsilylalkyl where the alkyl

1 group has 1 to 10 carbons, or a cycloalkyl group of  
2 5 to 10 carbons, or  $R_8$  is phenyl or lower  
3 alkylphenyl,  $R_9$  and  $R_{10}$  independently are hydrogen,  
4 an alkyl group of 1 to 10 carbons, or a cycloalkyl  
5 group of 5-10 carbons, or phenyl or lower  
6 alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower  
7 alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is divalent  
8 alkyl radical of 2-5 carbons.

9 16. A process in accordance with Claim 15 where  
10 the  $RAR_\alpha$  specific or selective retinoid compound is  
11 in accordance with formula (i).

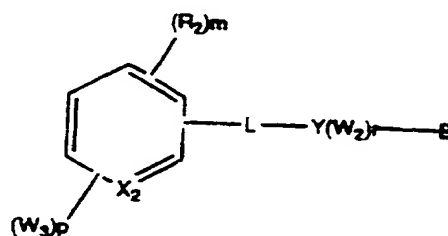
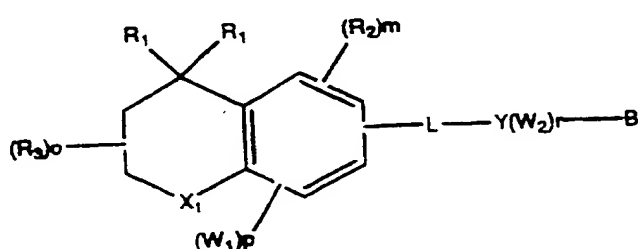
12 17. A process in accordance with Claim 15 where  
13 the formula the  $RAR_\alpha$  specific or selective retinoid  
14 compound is in accordance with formula (ii).

15 18. A process of administering to a mammal a  
16 retinoid compound which binds specifically or  
17 selectively to a  $RAR_\alpha$  retinoid receptors in  
18 preference over  $RAR_\beta$  and  $RAR_\gamma$  retinoid receptors, for  
19 the purpose of treating or preventing the disease or  
20 condition selected from acute monocytic leukemia,  
21 cervical carcinoma, myeloma, ovarian carcinomas,  
22 head and neck carcinomas, proliferative  
23 vitreoretinopathy (PVR) and age related macular  
24 degeneration (AMD) the retinoid compound being  
25 specific or selective for  $RAR_\alpha$  retinoid receptors in  
26 preference over  $RAR_\beta$  and  $RAR_\gamma$  retinoid receptors when  
27 in a binding assay the  $K_d$  value of binding to  $RAR_\alpha$   
28 receptors is approximately 500 times smaller than  
29 the  $K_d$  value for binding to  $RAR_\beta$  and  $RAR_\gamma$  retinoid  
30 receptors, the retinoid compound having the formula  
31 (i) or the formula (ii)

32

33

34



formula (i)

formula (ii)

where  $X_1$  is O or  $X_1$  is  $[C(R_1)_2]_n$  where  $n$  is an integer between 0 and 2;

$R_1$  is independently H or alkyl of 1 to 6 carbons;

$R_2$  is independently hydrogen, or lower alkyl of 1 to 6 carbons;

$R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

$m$  is an integer having the value of 0 - 5;

$o$  is an integer having the value of 0 - 4;

$p$  is an integer having the value of 0 - 2;

$r$  is an integer having the value 0 - 2;

$X_2$  is N or CH;

$Y$  is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl, naphthyl and heteroaryl groups being optionally substituted with one or two  $R_2$  groups;

$W_1$  is a substituent selected independently from the group consisting of F, Br, Cl, I, fluoro substituted  $C_{1-6}$  alkyl,  $NO_2$ , and OH, with the provisos that:

(i) when the compound is in accordance with



1 formula (i) and Z is O then the sum of p and r is at  
2 least 1 and W<sub>1</sub> is not a fluoro group in the 3  
3 position of a tetrahydronaphthalene ring;

4 (ii) when the compound is in accordance with  
5 formula (ii) and r is zero and p is 1 and W<sub>1</sub> is OH  
6 then the OH group is positioned α to the L group;

7 W<sub>2</sub> is a substituent selected independently from  
8 the group consisting of F, Br, Cl, I, fluoro  
9 substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH;

10 W<sub>3</sub> is a substituent selected independently from  
11 the group consisting of F, Br, Cl, I, C<sub>1-6</sub>alkyl,  
12 fluoro substituted C<sub>1-6</sub> alkyl, NO<sub>2</sub>, and OH with the  
13 proviso that when the compound is in accordance with  
14 Formula 2 and X<sub>2</sub> is CH and r is 0 then p is not 0 and  
15 at least one W<sub>3</sub> group is not alkyl;

16 L is -(C=Z)-NH- or -NH-(C=Z)-

17 Z is O or S, and

18 B is COOH or a pharmaceutically acceptable salt  
19 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>,  
20 CHO, CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O,  
21 where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group  
22 containing 1 to 5 carbons, R<sub>8</sub> is an alkyl group of 1  
23 to 10 carbons or trimethylsilylalkyl where the alkyl  
24 group has 1 to 10 carbons, or a cycloalkyl group of  
25 5 to 10 carbons, or R<sub>8</sub> is phenyl or lower  
26 alkylphenyl, R<sub>9</sub> and R<sub>10</sub> independently are hydrogen,  
27 an alkyl group of 1 to 10 carbons, or a cycloalkyl  
28 group of 5-10 carbons, or phenyl or lower  
29 alkylphenyl, R<sub>11</sub> is lower alkyl, phenyl or lower  
30 alkylphenyl, R<sub>12</sub> is lower alkyl, and R<sub>13</sub> is divalent  
31 alkyl radical of 2-5 carbons.

32 19. A process in accordance with Claim 18 where  
33 the RAR<sub>a</sub> specific or selective retinoid compound is  
34 in accordance with formula (i), and Y is phenyl.

1 20. A process in accordance with Claim 19 where the  
2 RAR<sub>α</sub> specific or selective retinoid compound is  
3 selected from the group consisting of:

4 ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-  
5 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be  
6 nzoate;

7 2-fluoro-4-[(5',6',7',8'-tetrahydro-  
8 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be  
9 nzoic acid;

10 ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-4'-  
11 bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam  
12 oyl]benzoate;

13 2-fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-  
14 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be  
15 nzoic acid;

16 ethyl  
17 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman  
18 -6'-yl)carbamoyl]benzoate;

19  
20 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman  
21 - 6'-yl)carbamoyl]benzoic acid;

22 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
23 trifluoromethylchroman-6'-yl)carbamoyl] benzoate;

24 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
25 trifluoro-methylchroman-6'-yl)carbamoyl] benzoic  
26 acid;

27 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
28 azidochroman-6'-yl)carbamoyl]benzoate;

29 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
30 azidochroman- 6'-yl)carbamoyl]benzoic acid;

31 ethyl 2-fluoro-4-[(2', 2', 4', 4'-tetramethyl-  
32 8'-iodochroman-6'-yl)carbamoyl]benzoate;

33 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-  
34 iodochroman-6'-yl)carbamoyl]benzoic acid;

1 ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-  
2 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate,  
3 and

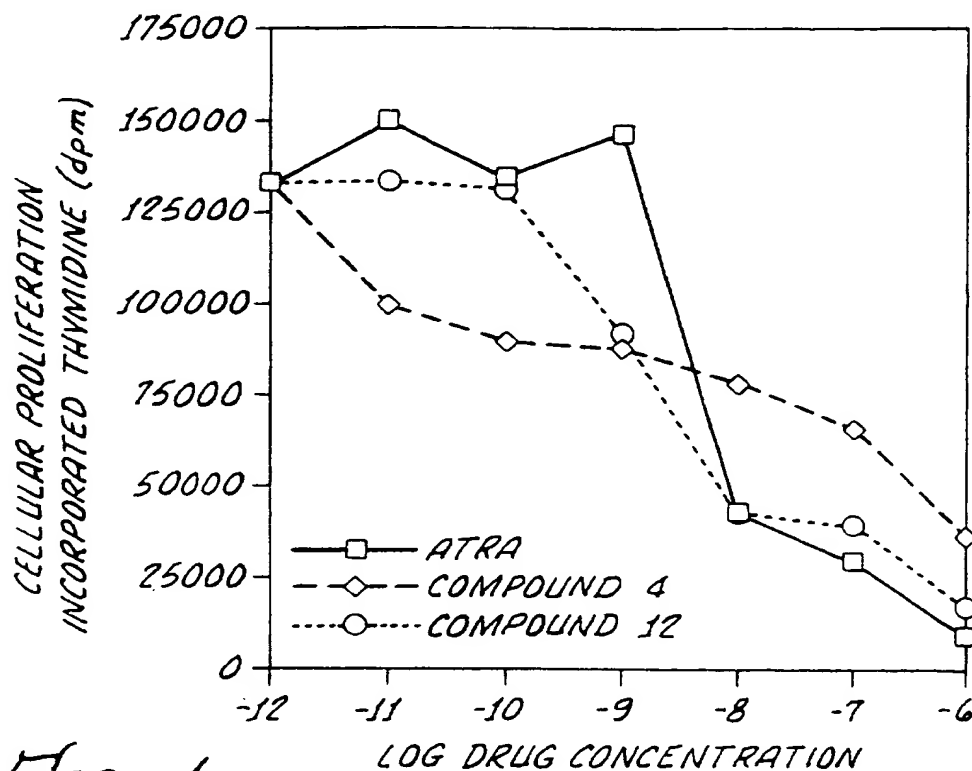
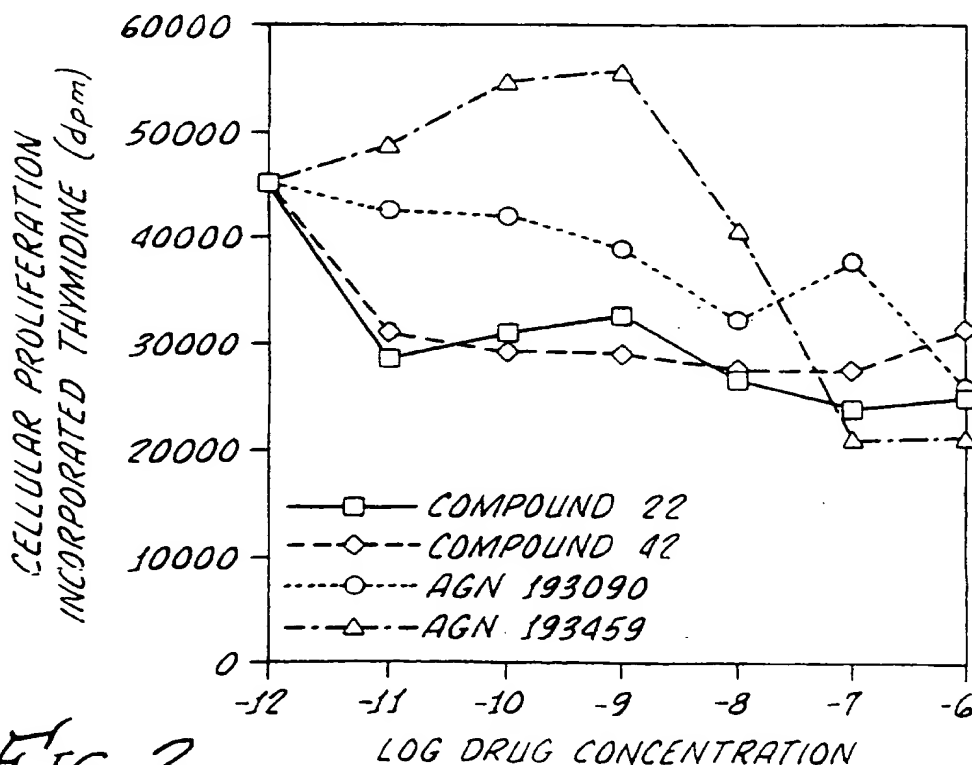
4 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-  
5 tetramethylnaphthalen-2'-yl)thiocarbamoyl]benzoic  
6 acid.

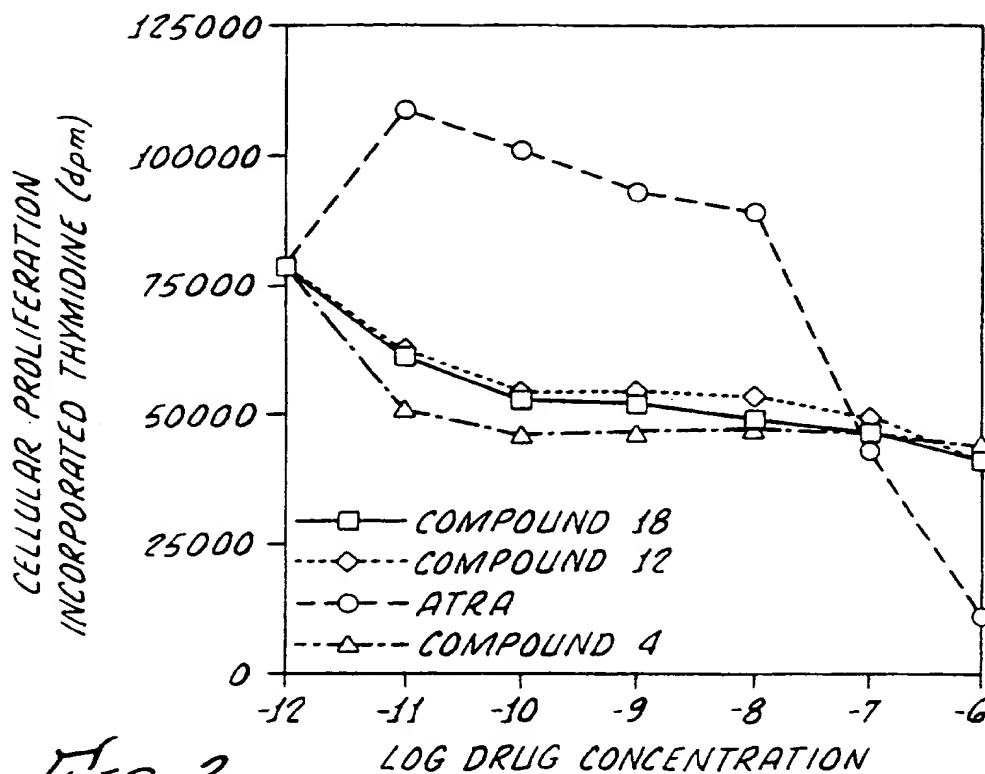
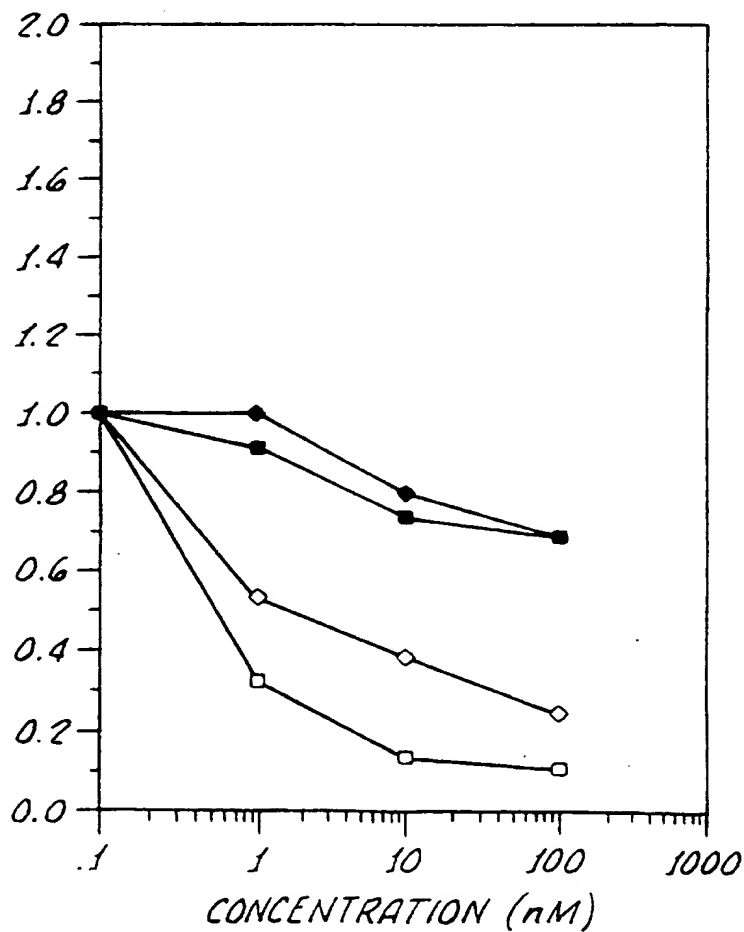
7 21. A process in accordance with Claim 18 where  
8 the RAR<sub>α</sub> specific or selective retinoid compound is  
9 in accordance with formula (ii), and Y is phenyl.

10 22. A process in accordance with Claim 19 where  
11 the RAR<sub>α</sub> specific or selective retinoid compound  
12 is:

13 ethyl 2-fluoro-4-[(2',6'-di-tert-butylpyrid-4'-  
14 yl)carbamoyl]benzoate, or

15 2-fluoro-4-[(2',6'-di-t-butylpyrid-4'-  
16 yl)carbamoyl]benzoic acid.

FIG. 1.FIG. 2.

FIG. 3.FIG. 4.

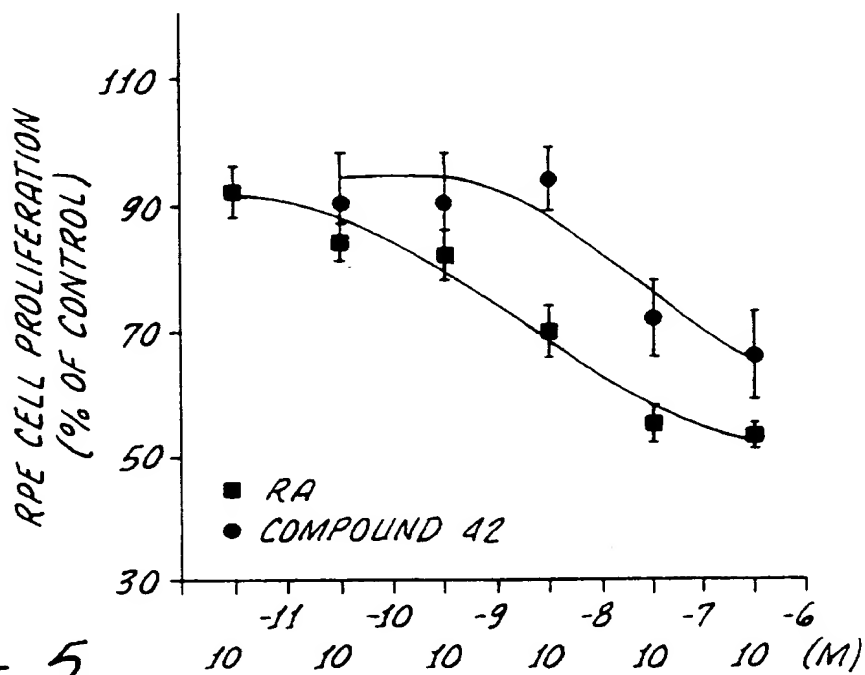


FIG. 5.

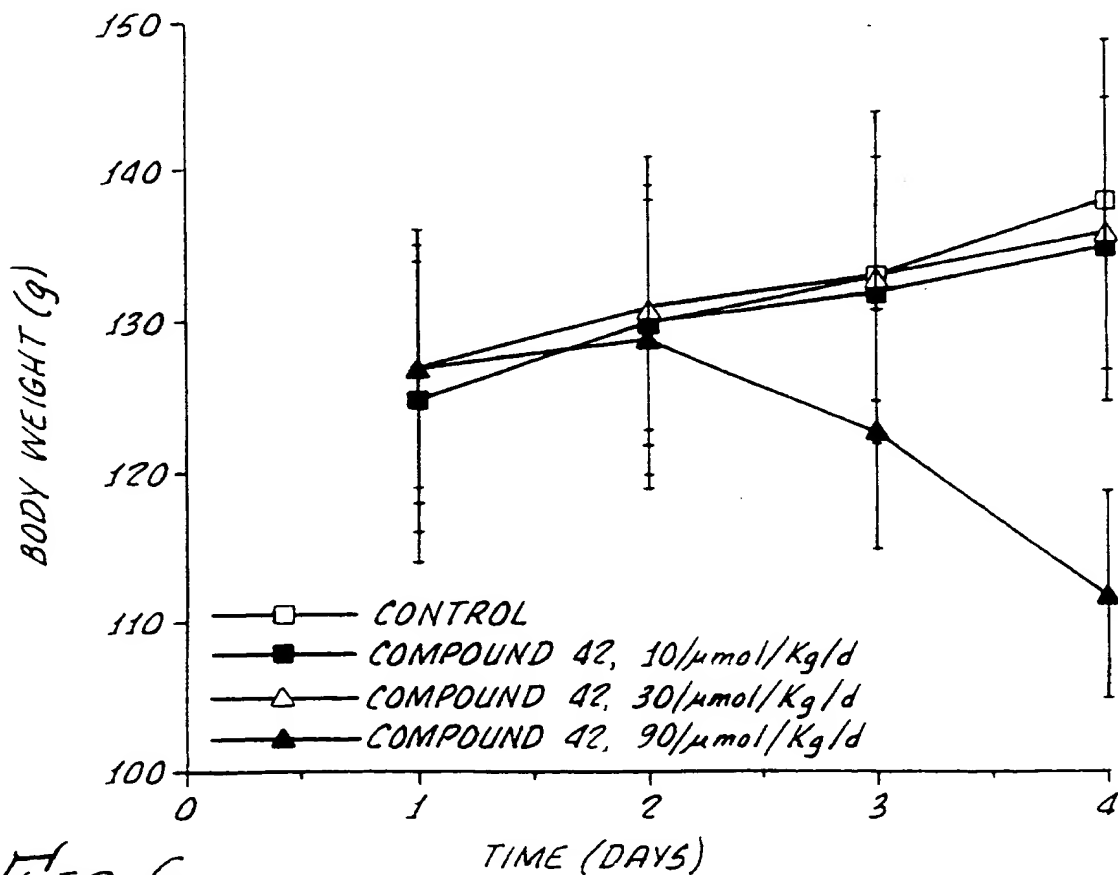
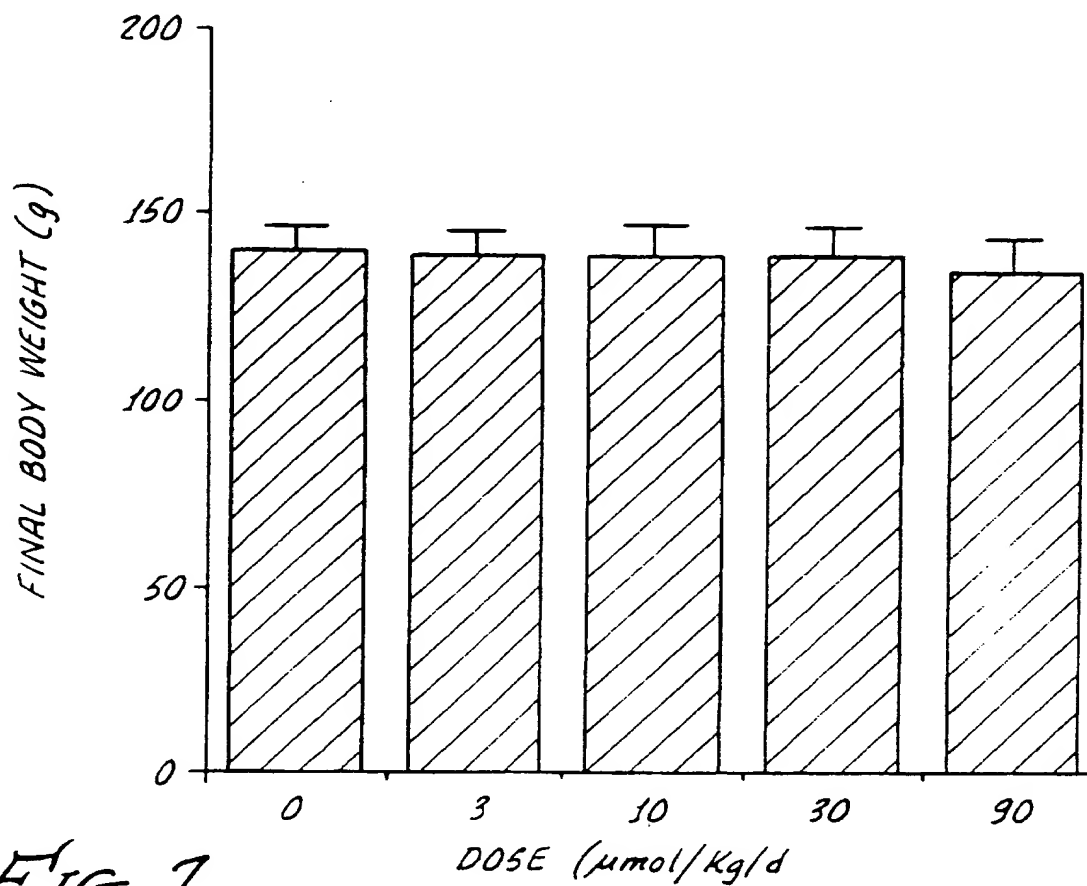
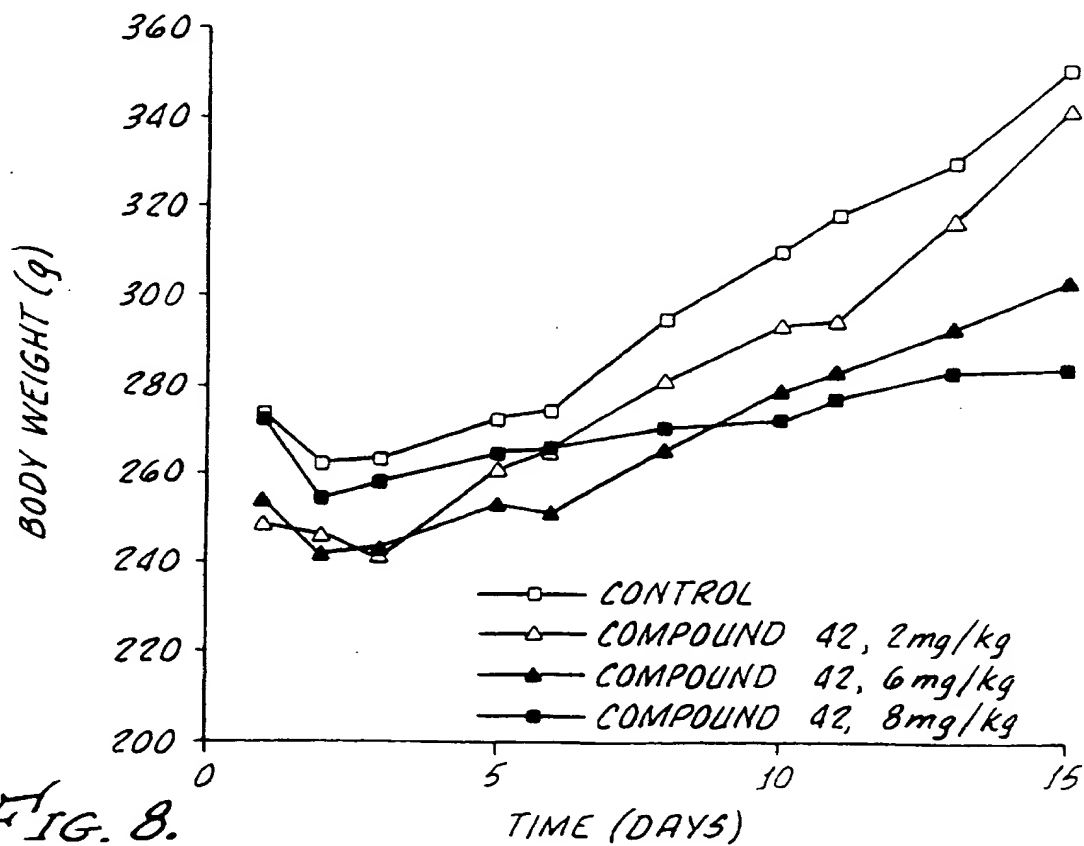


FIG. 6.

FIG. 7.FIG. 8.





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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/19, 31/215, 31/34, 31/44</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 97/24116</b> <b>(43) International Publication Date:</b> 10 July 1997 (10.07.97)
<b>(21) International Application Number:</b> PCT/US96/20511 <b>(22) International Filing Date:</b> 16 December 1996 (16.12.96) <b>(30) Priority Data:</b> 08/580,553 29 December 1995 (29.12.95) US <b>(71) Applicant:</b> ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US). <b>(72) Inventors:</b> TENG, Min; 2 Dove Street, Aliso Viejo, CA 92656 (US). DUONG, Tien, T.; Apartment 15C, 13 Bearpaw, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). <b>(74) Agents:</b> BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, T-2,2-E, P.O. Box 19534, Irvine, CA 92623-9534 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <b>(88) Date of publication of the international search report:</b> 13 November 1997 (13.11.97)
<b>(54) Title:</b> METHODS OF TREATMENT WITH COMPOUNDS HAVING RAR <sub>α</sub> RECEPTOR SPECIFIC OR SELECTIVE ACTIVITY		
<b>(57) Abstract</b>		
<p>Retinoid compounds which act specifically or selectively on RAR<sub>α</sub> receptor subtypes in preference over RAR<sub>β</sub> and RAR<sub>γ</sub> receptor subtypes, possess desirable pharmaceutical properties associated with retinoids, and are particularly suitable for treatment of tumors, such as acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas and head and neck carcinomas, without having one or more undesirable side effects of retinoids, such as inducement of weight loss, mucocutaneous toxicity, skin irritation and teratogenicity.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/20511

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/19 A61K31/215 A61K31/34 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 03713 A (SALK INST FOR BIOLOGICAL STUDI) 4 March 1993  see page 9, line 4 - line 31; claims 1-15 --- -/-	1-4, 6-12, 14-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

13 May 1997

Date of mailing of the international search report

30.09.97

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Seegert, K

# INTERNATIONAL SEARCH REPORT

Interr. Application No

PCT/US 96/20511

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 121, no. 9, 1994 Columbus, Ohio, US; abstract no. 108128d, XP002030814 see abstract & YU, BAOXIN ET AL: "Synthesis of p-substituted benzoylaminobenzoic acid (methyl esters) and its differentiation induction activities of human promyelocytic leukemia cells HL-60" HUAXI YIKE DAXUE XUEBAO, vol. 25, no. 1, 1994, pages 30-34, ---	1-4, 6-12, 14-22
Y	DATABASE WPI Section Ch, Week 9416 Derwent Publications Ltd., London, GB; Class B05, AN 94-128759 XP002030803 & JP 06 072 866 A (CHUGOKU IGAKUKAGAKUIN YAKUBUTSU KENKYUSH) , 15 March 1994 see abstract ---	1-4, 6-12, 14-22
Y	EP 0 514 269 A (CIRD GALDERMA) 19 November 1992  see page 3, line 3 - page 3, line 9; claims 1-21 especially claim 16, ex. 15 ---	1-4, 6-12, 14-22
Y	EP 0 350 846 A (HOFFMANN LA ROCHE) 17 January 1990  see page 5, line 43 - page 6, line 35; claims 1-18 ---	1-4, 6-12, 14-22
Y	US 5 420 145 A (SHUDO KOICHI) 30 May 1995  see column 3, line 65 - column 4, line 29; claims 1-4 ---	1-4, 6-12, 14-22
Y	EP 0 170 105 A (SHUDO KOICHI ;SUMITOMO PHARMA (JP); YOSHITOMI PHARMACEUTICAL (JP)) 5 February 1986 see claims 1-11 ---	1-4, 6-12, 14-22
P,Y	WO 96 32101 A (TAIHO PHARMACEUTICAL CO LTD ;SHIBATA JIRO (JP); WIERZBA KONSTANTY) 17 October 1996 see abstract ---	1-4, 6-12, 14-22
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/20511

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KAGECHIKA H ET AL: "RETINO BENZOIC ACIDS STRUCTURE-ACTIVITY RELATIONSHIPS OF AROMATIC AMIDES WITH RETINOIDAL ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 11, November 1988, pages 2182-2192, XP000608417 see tables I-VI see page 2187, left-hand column, last paragraph - page 2188, left-hand column ---	1-4, 6-12, 14-22
P,Y	MIN TENG ET AL: "Identification of a Retinoic Acid Receptor alpha Subtype Specific Agonist" J. MED. CHEM., vol. 39, no. 16, 2 August 1996, pages 3035-3038, XP000652115 see the whole document -----	1-4, 6-12, 14-22

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 20511

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annex.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 6-12, 14-22 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96 20511

FURTHER INFORMATION CONTINUED FROM PCT/SA210

1. The use of a RAR alpha selective agonist for the prevention/treatment of acute monocytic leukemia, cervical carcinoma, myeloma, ovarian carcinomas, head and neck carcinomas (respective portions of Claims 1- 4, 6- 12, 14 - 22)
2. The use of a RAR alpha selective agonist for the prevention/treatment of proliferative vitreoretinopathy (PVR), age related macular degeneration (AMD), diseases of the eye, retinal detachment, dry eye, other corneopathies (respective portions of Claims 1 - 22)
3. The use of a RAR alpha selective agonist for the prevention/treatment of actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses, eczema, atopic dermatitis, Darriers disease, lichen planus, skin pigmentation, age and photo damage to the skin, premalignant and malignant hyperproliferative diseases, Kaposi's sarcoma (respective portions of Claims 1, 2, 4 - 13, 15- 22)
4. The use of a RAR alpha selective agonist for the prevention/treatment of cardiovascular diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)
5. The use of a RAR alpha selective agonist for the prevention/treatment of dyslipidemias (respective portions of Claims 1, 2, 4 - 13, 15- 22)
6. The use of a RAR alpha selective agonist for the prevention of post-angioplasty restenosis (respective portions of Claims 1, 2, 4 - 13, 15- 22)

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96 20511

FURTHER INFORMATION CONTINUED FROM PCT/ISA210

7. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with human papilloma virus (HPV) (respective portions of Claims 1, 2, 4 - 13, 15- 22)

8. The use of a RAR alpha selective agonist for the for the prevention/treatment of inflammatory diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)

9. The use of a RAR alpha selective agonist for the prevention/treatment of neurodegenerative diseases (respective portions of Claims 1, 2, 4 - 13, 15- 22)

10. The use of a RAR alpha selective agonist for the prevention/treatment of improper pituitary function (respective portions of Claims 1, 2, 4 - 13, 15- 22)

11. The use of a RAR alpha selective agonist for the prevention/treatment of insufficient hair growth (respective portions of Claims 1, 2, 4 - 13, 15- 22)

12. The use of a RAR alpha selective agonist for the prevention/treatment of diseases associated with the immune system (respective portions of Claims 1, 2, 4 - 13, 15- 22)

13. The use of a RAR alpha selective agonist for wound healing (respective portions of Claims 1, 2, 4 - 13, 15- 22)

The search has been limited to the subject-matter of item 1.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/20511

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